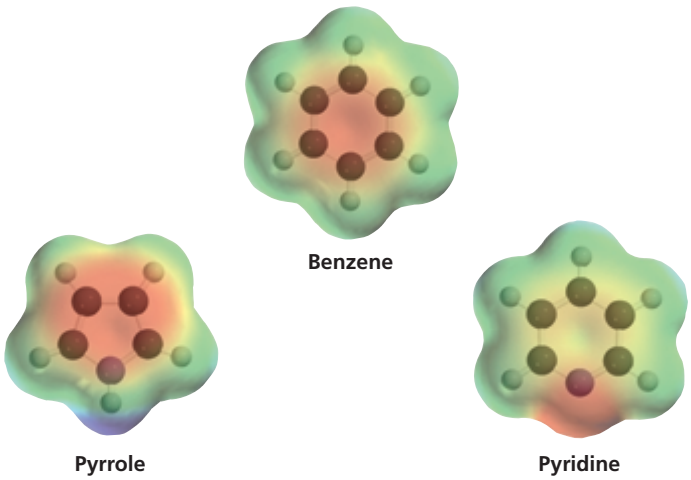
15 Aromaticity • Reactions of Benzene



The compound we know as benzene was first isolated in 1825 by Michael Faraday, who extracted the compound from a liquid residue obtained after heating whale oil under pressure to produce a gas used to illuminate buildings in London. Because of its origin, chemists suggested that it should be called "pheno" from the Greek word *phainein* ("to shine").

In 1834, Eilhardt Mitscherlich correctly determined benzene's molecular formula (C_6H_6) and decided to call it benzin because of its relationship to benzoic acid, a known substituted form of the compound. Later its name was changed to benzene.

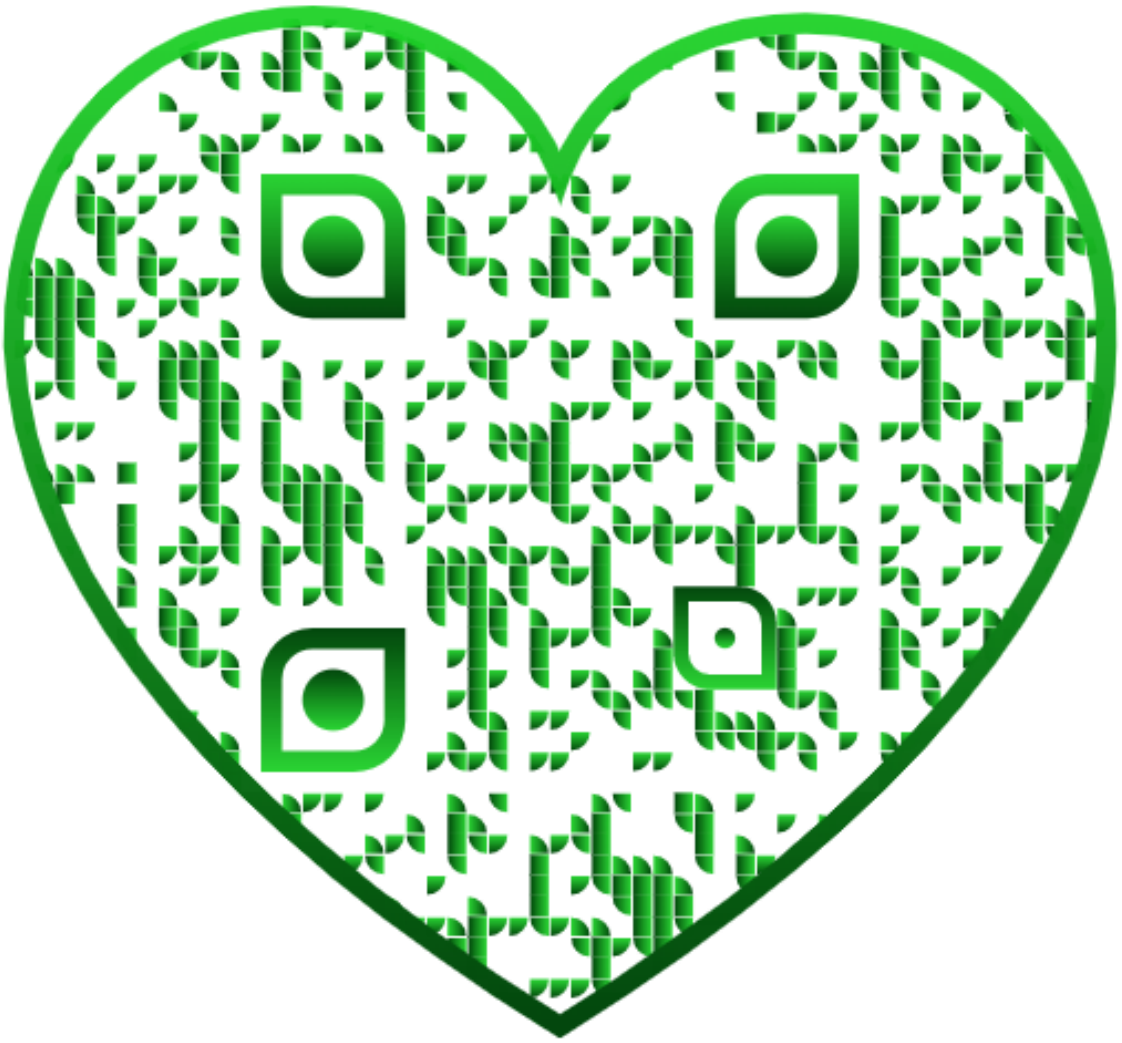
Compounds like benzene, which have relatively few hydrogens in relation to the number of carbons, are typically found in oils produced by trees and other plants. Early chemists called such compounds **aromatic** compounds because of their pleasing fragrances. In this way, they were distinguished from **aliphatic** compounds, with higher hydrogen-to-carbon ratios, that were obtained from the chemical degradation of fats. The chemical meaning of the word "aromatic" now signifies certain kinds of chemical structures. We will now examine the criteria that a compound must satisfy to be classified as aromatic.

Michael Faraday (1791–1867) *was born in England, a son of a blacksmith. At the age of 14, he was apprenticed to a bookbinder and educated himself by reading the books that he bound. He became an assistant to Sir Humphry Davy in 1812 and taught himself chemistry. In 1825, he became the director of a laboratory at the Royal Institution, and, in 1833, he became a professor of chemistry there. He is best known for his work on electricity and magnetism.*

Eilhardt Mitscherlich (1794–1863) *was born in Germany. He studied oriental languages at the University of Heidelberg and the Sorbonne, where he concentrated on Farsi, hoping that Napoleon would include him in a delegation he intended to send to Persia. That ambition ended with Napoleon's defeat. Mitscherlich returned to Germany to study science, simultaneously receiving a doctorate in Persian studies. He was a professor of chemistry at the University of Berlin.*

15.1 Criteria for Aromaticity

In Chapter 7, we saw that benzene is a planar, cyclic compound with a cyclic cloud of delocalized electrons above and below the plane of the ring (Figure 15.1). Because its π electrons are delocalized, all the C—C bonds have the same length—partway between the length of a typical single and a typical double bond. We also saw that benzene is a particularly stable compound because it has an unusually large resonance energy (36 kcal/mol or 151 kJ/mol). Most compounds with delocalized electrons



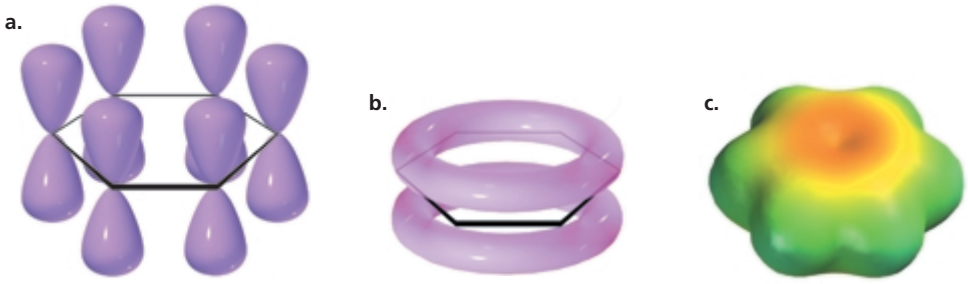


Figure 15.1
(a) Each carbon of benzene has a *p* orbital. (b) The overlap of the *p* orbitals forms a cloud of π electrons above and below the plane of the benzene ring. (c) The electrostatic potential map for benzene shows that all the carbon–carbon bonds have the same electron density.

have much smaller resonance energies. Compounds such as benzene with unusually large resonance energies are called aromatic compounds. How can we tell whether a compound is aromatic by looking at its structure? In other words, what structural features do aromatic compounds have in common?

Aromatic compounds are particularly stable.

To be classified as aromatic, a compound must meet both of the following criteria:

1. *It must have an uninterrupted cyclic cloud of π electrons* (often called a π cloud) *above and below the plane of the molecule.* Let's look a little more closely at what this means:
   For the π cloud to be cyclic, *the molecule must be cyclic*.
   For the π cloud to be uninterrupted, *every atom in the ring must have a* p *orbital*.
   For the π cloud to form, each *p* orbital must overlap with the *p* orbitals on either side of it. Therefore, *the molecule must be planar*.
2. *The π cloud must contain an odd number of pairs of π electrons.*

Benzene is an aromatic compound because it is cyclic and planar, every carbon in the ring has a *p* orbital, and the π cloud contains *three* pairs of π electrons.

For a compound to be aromatic, it must be cyclic and planar and have an uninterrupted cloud of π electrons. The π cloud must contain an odd number of pairs of π electrons.

The German chemist Erich Hückel was the first to recognize that an aromatic compound must have an odd number of pairs of π electrons. In 1931, he described this requirement by what has come to be known as **Hückel's rule**, or the **$4n + 2$ rule**. The rule states that for a planar, cyclic compound to be aromatic, its uninterrupted π cloud must contain $(4n + 2)\pi$ electrons, where *n* is any whole number. According to Hückel's rule, then, an aromatic compound must have 2 $(n = 0)$, 6 $(n = 1)$, 10 $(n = 2)$, 14 $(n = 3)$, 18 $(n = 4)$, etc., π electrons. Because there are two electrons in a pair, Hückel's rule requires that an aromatic compound have 1, 3, 5, 7, 9, etc., pairs of π electrons. Thus, Hückel's rule is just a mathematical way of saying that an aromatic compound must have an *odd* number of pairs of π electrons.

Erich Hückel (1896–1980) *was born in Germany. He was a professor of chemistry at the University of Stuttgart and at the University of Marburg.*

PROBLEM 1◆

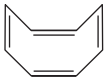
a. What is the value of *n* in Hückel's rule when a compound has nine pairs of π electrons?
b. Is such a compound aromatic?

15.2 Aromatic Hydrocarbons

Monocyclic hydrocarbons with alternating single and double bonds are called **annulenes**. A prefix in brackets denotes the number of carbons in the ring. Cyclobutadiene, benzene, and cyclooctatetraene are examples.

cyclobutadiene
[4]-annulene

benzene
[6]-annulene


cyclooctatetraene
[8]-annulene

3-D Molecules: Cyclobutadiene; Benzene; Cyclooctatetraene

Cyclobutadiene has two pairs of π electrons, and cyclooctatetraene has four pairs of π electrons. Unlike benzene, these compounds are *not* aromatic because they have an *even* number of pairs of π electrons. There is an additional reason why cyclooctatetraene is not aromatic—it is not planar but, instead, tub-shaped. Earlier, we saw that, for an eight-membered ring to be planar, it must have bond angles of 135° (Chapter 2, Problem 28), and we know that sp^2 carbons have 120° bond angles. Therefore, if cyclooctatetraene were planar, it would have considerable angle strain. Because cyclobutadiene and cyclooctatetraene are not aromatic, they do not have the unusual stability of aromatic compounds.

Now let's look at some other compounds and determine whether they are aromatic. Cyclopropene is not aromatic because it does not have an uninterrupted ring of *p* orbital-bearing atoms. One of its ring atoms is sp^3 hybridized, and only sp^2 and *sp* hybridized carbons have *p* orbitals. Therefore, cyclopropene does not fulfill the first criterion for aromaticity.

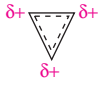
cyclopropene | cyclopropenyl cation | cyclopropenyl anion

Tutorial: Aromaticity

The cyclopropenyl cation is aromatic because it has an uninterrupted ring of *p* orbital-bearing atoms and the π cloud contains *one* (an odd number) pair of delocalized π electrons. The cyclopropenyl anion is not aromatic because although it has an uninterrupted ring of *p* orbital-bearing atoms, its π cloud has *two* (an even number) pairs of π electrons.

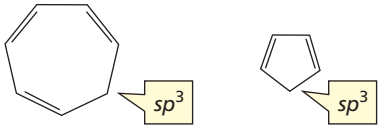
When drawing resonance contributors, remember that only electrons move, atoms never move.

resonance contributors of the cyclopropenyl cation



resonance hybrid

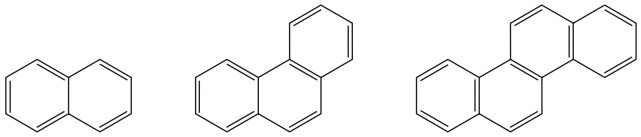
Cycloheptatriene is not aromatic. Although it has the correct number of pairs of π electrons (three) to be aromatic, it does not have an uninterrupted ring of *p* orbital-bearing atoms because one of the ring atoms is sp^3 hybridized. Cyclopentadiene is also not aromatic: It has an even number of pairs of π electrons (two pairs), *and* it does not have an uninterrupted ring of *p* orbital-bearing atoms. Like cycloheptatriene, cyclopentadiene has an sp^3 hybridized carbon.



cycloheptatriene | cyclopentadiene

3-D Molecules: Phenanthrene; Naphthalene

The criteria for determining whether a monocyclic hydrocarbon compound is aromatic can also be used to determine whether a polycyclic hydrocarbon compound is aromatic. Naphthalene (five pairs of π electrons), phenanthrene (seven pairs of π electrons), and chrysene (nine pairs of π electrons) are aromatic.



naphthalene | phenanthrene | chrysene

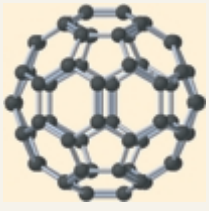
BUCKYBALLS AND AIDS

In addition to diamond and graphite (Section 1.1), a third form of pure carbon was discovered while scientists were conducting experiments designed to understand how long-chain molecules are formed in outer space. R. E. Smalley, R. F. Curl, Jr., and H. W. Kroto, the discoverers of this new form of carbon, shared the 1996 Nobel Prize in chemistry for their discovery. They named this new form buckminsterfullerene (often shortened to fullerene) because it reminded them of the geodesic domes popularized by R. Buckminster Fuller, an American architect and philosopher. The substance is nicknamed "buckyball." Consisting of a hollow cluster of 60 carbons, fullerene is the most symmetrical large molecule known. Like graphite, fullerene has only sp^2 hybridized carbons, but instead of being arranged in layers, the carbons are arranged in rings, forming a hollow cluster of 60 carbons that fit together like the seams of a soccer ball. Each molecule has 32 interlocking rings (20 hexagons and 12 pentagons). At first glance, fullerene would appear to be aromatic because of its benzene-like rings. However, it does not undergo electrophilic substitution reactions; instead, it undergoes electrophilic addition reactions like an alkene. Fullerene's lack of aromaticity is apparently caused by the curvature of the ball, which prevents the molecule from fulfilling the first criterion for aromaticity—that it must be planar.

Buckyballs have extraordinary chemical and physical properties. They are exceedingly rugged and are capable of surviving the extreme temperatures of outer space. Because they are essentially hollow cages, they can be manipulated to make materials never before known. For example, when a buckyball is "doped" by inserting potassium or cesium into its cavity, it becomes an excellent organic superconductor. These molecules are presently being studied for use in many other applications, such as new polymers and catalysts and new drug delivery systems. The discovery of buckyballs is a strong reminder of the technological advances that can be achieved as a result of conducting basic research.

Scientists have even turned their attention to buckyballs in their quest for a cure for AIDS. An enzyme that is required for HIV to reproduce exhibits a nonpolar pocket in its three-dimensional structure. If this pocket is blocked, the production of the virus ceases. Because buckyballs are nonpolar and have approximately the same diameter as the pocket of the enzyme, they are being considered as possible blockers. The first step in pursuing this possibility was to equip the buckyball with polar side chains to make it water soluble so that it could flow through the bloodstream. Scientists have now modified the side chains so that they bind to the enzyme. It's still a long way from a cure for AIDS, but this represents one example of the many and varied approaches that scientists are taking to find a cure for this disease.

A geodesic dome

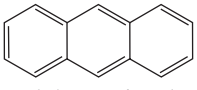


C_{60}
buckminsterfullerene
"buckyball"

PROBLEM 2◆

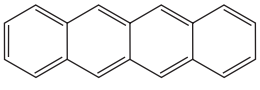
Which of the following compounds are aromatic?

a.

b. 

c. cycloheptatrienyl cation

d.

e. 

f.

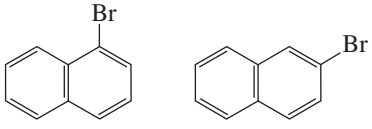
g. cyclononatetraenyl anion

h. $CH_2{=}CHCH{=}CHCH{=}CH_2$

PROBLEM 3 SOLVED

a. How many monobromonaphthalenes are there?
b. How many monobromophenanthrenes are there?

SOLUTION TO 3a There are two monobromonaphthalenes. Substitution cannot occur at either of the carbons shared by both rings, because those carbons are not bonded to a hydrogen. Naphthalene is a flat molecule, so substitution for a hydrogen at any other carbon will result in one of the compounds shown.



Richard E. Smalley *was born in 1943 in Akron, Ohio. He received a B.S. from the University of Michigan and a Ph.D. from Princeton University. He is a professor of chemistry at Rice University.*

Robert F. Curl, Jr., *was born in Texas in 1933. He received a B.A. from Rice University and a Ph.D. from the University of California, Berkeley. He is a professor of chemistry at Rice University.*

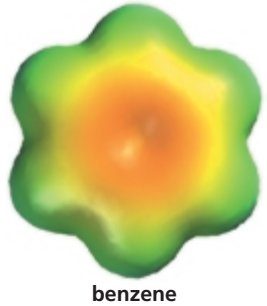
Sir Harold W. Kroto *was born in 1939 in England and is a professor of chemistry at the University of Sussex.*

3-D Molecules:
1-Chloronaphthalene;
2-Chloronaphthalene

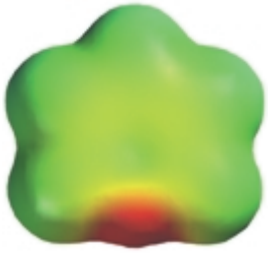
PROBLEM 4

The [10]- and [12]-annulenes have been synthesized, and neither has been found to be aromatic. Explain.

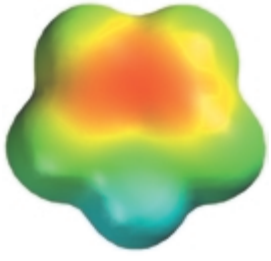
15.3 Aromatic Heterocyclic Compounds



benzene



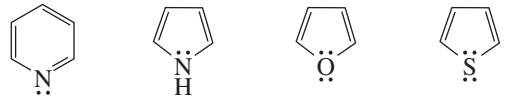
pyridine



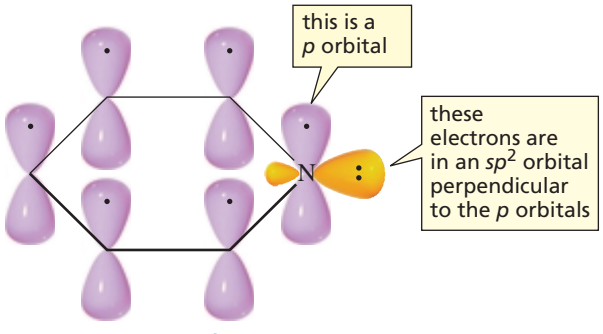
pyrrole

A compound does not have to be a hydrocarbon to be aromatic. Many *heterocyclic compounds* are aromatic. A **heterocyclic compound** is a cyclic compound in which one or more of the ring atoms is an atom other than carbon. A ring atom that is not carbon is called a **heteroatom**. The name comes from the Greek word *heteros*, which means "different." The most common heteroatoms found in heterocyclic compounds are N, O, and S.

heterocyclic compounds

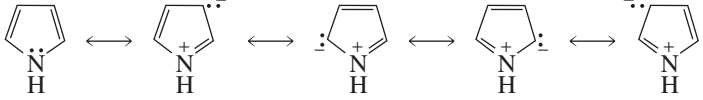


Pyridine is an aromatic heterocyclic compound. Each of the six ring atoms of pyridine is sp^2 hybridized, which means that each has a *p* orbital; and the molecule contains three pairs of π electrons. Don't be confused by the lone-pair electrons on the nitrogen; they are not π electrons. Because nitrogen is sp^2 hybridized, it has three sp^2 orbitals and a *p* orbital. The *p* orbital is used to form the π bond. Two of nitrogen's sp^2 orbitals overlap the sp^2 orbitals of adjacent carbon atoms, and nitrogen's third sp^2 orbital contains the lone pair.

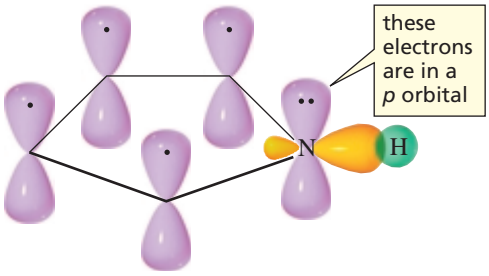


orbital structure of pyridine

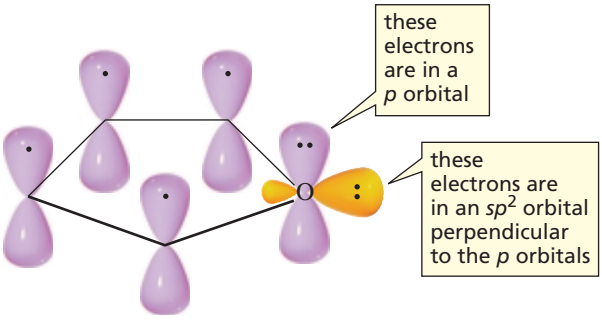
It is not immediately apparent that the electrons represented as lone-pair electrons on the nitrogen atom of pyrrole are π electrons. The resonance contributors, however, show that the nitrogen atom is sp^2 hybridized and uses its three sp^2 orbitals to bond to two carbons and one hydrogen. The lone-pair electrons are in a *p* orbital that overlaps the *p* orbitals on adjacent carbons, forming a π bond—thus, they are π electrons. Pyrrole, therefore, has three pairs of π electrons and is aromatic.



resonance contributors of pyrrole

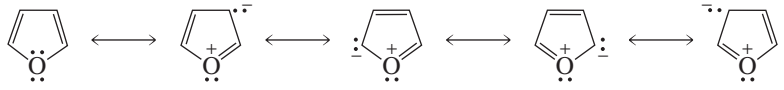


orbital structure of pyrrole



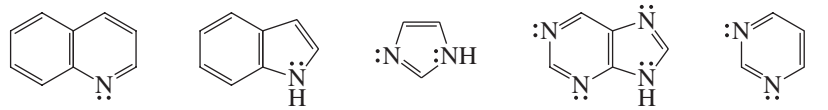
orbital structure of furan

Similarly, furan and thiophene are stable aromatic compounds. Both the oxygen in the former and the sulfur in the latter are sp^2 hybridized and have one lone pair in an sp^2 orbital. The second lone pair is in a p orbital that overlaps the p orbitals of adjacent carbons, forming a π bond. Thus, they are π electrons.



resonance contributors of furan

Quinoline, indole, imidazole, purine, and pyrimidine are other examples of heterocyclic aromatic compounds. The heterocyclic compounds discussed in this section are examined in greater detail in Chapter 21.



quinoline indole imidazole purine pyrimidine

PROBLEM 5◆

In what orbitals are the electrons represented as lone pairs when drawing the structures of quinoline, indole, imidazole, purine, and pyrimidine?

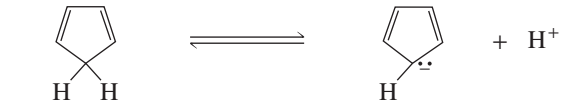
PROBLEM 6

Answer the following questions by examining the electrostatic potential maps on p. 598:

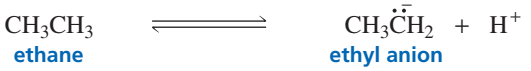
a. Why is the bottom part of the electrostatic potential map of pyrrole blue?
b. Why is the bottom part of the electrostatic potential map of pyridine red?
c. Why is the center of the electrostatic potential map of benzene more red than the center of the electrostatic potential map of pyridine?

15.4 Some Chemical Consequences of Aromaticity

The pK_a of cyclopentadiene is 15, which is extraordinarily acidic for a hydrogen that is bonded to an sp^3 hybridized carbon. Ethane, for example, has a pK_a of 50.



cyclopentadiene pK_a = 15 — cyclopentadienyl anion

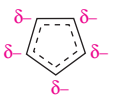


ethane pK_a = 50 — ethyl anion

Tutorial:
Aromaticity and acidity

Why is the pK_a of cyclopentadiene so much lower than that of ethane? To answer this question, we must look at the stabilities of the anions that are formed when the compounds lose a proton. (Recall that the strength of an acid is determined by the stability of its conjugate base: The more stable its conjugate base, the stronger is the acid; see Section 1.18.) All the electrons in the ethyl anion are localized. In contrast, the anion that is formed when cyclopentadiene loses a proton fulfills the requirements for aromaticity: It is cyclic and planar, each atom in the ring has a *p* orbital, and the π cloud has three pairs of delocalized π electrons. The negatively charged carbon in the cyclopentadienyl anion is sp^2 hybridized because if it were sp^3 hybridized, the ion would not be aromatic. The resonance hybrid shows that all the carbons in the cyclopentadienyl anion are equivalent. Each carbon has exactly one-fifth of the negative charge associated with the anion.

resonance contributors of the cyclopentadienyl anion



resonance hybrid

As a result of its aromaticity, the cyclopentadienyl anion is an unusually stable carbanion. This is why cyclopentadiene has an unusually low pK_a. In other words, it is the stability conveyed by the aromaticity of the cyclopentadienyl anion that makes the hydrogen much more acidic than hydrogens bonded to other sp^3 carbons.

PROBLEM 7◆

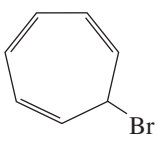
Predict the relative pK_a values of cyclopentadiene and cycloheptatriene.

PROBLEM 8

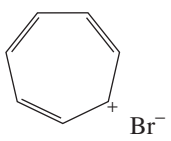
a. Draw arrows to show the movement of electrons in going from one resonance contributor to the next in
   1. the cyclopentadienyl anion
   2. pyrrole

b. How many ring atoms share the negative charge in
   1. the cyclopentadienyl anion?
   2. pyrrole?

Another example of the influence of aromaticity on chemical reactivity is the unusual chemical behavior exhibited by cycloheptatrienyl bromide. Recall from Section 2.9 that alkyl halides tend to be relatively nonpolar covalent compounds—they are soluble in nonpolar solvents and insoluble in water. Cycloheptatrienyl bromide, however, is an alkyl halide that behaves like an ionic compound—it is insoluble in nonpolar solvents, but readily soluble in water.

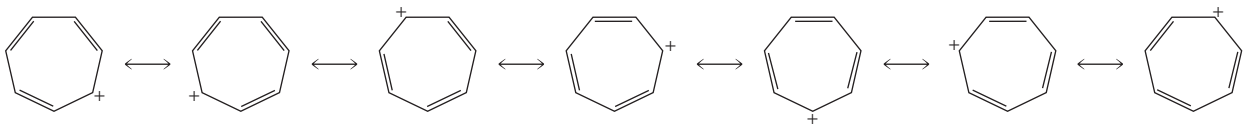


covalent
cycloheptatrienyl bromide

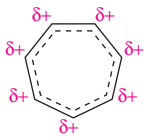


ionic
cycloheptatrienyl bromide
tropylium bromide

Cycloheptatrienyl bromide is an ionic compound because its cation is aromatic. The alkyl halide is *not* aromatic in the covalent form because it has an sp^3 hybridized carbon, so it does *not* have an uninterrupted ring of p orbital-bearing atoms. In the ionic form, however, the cycloheptatrienyl cation (also known as the tropylium cation) *is* aromatic because it is a planar cyclic ion, all the ring atoms are sp^2 hybridized (which means that each ring atom has a p orbital), and it has three pairs of delocalized π electrons. The stability associated with the aromatic cation causes the alkyl halide to exist in the ionic form.



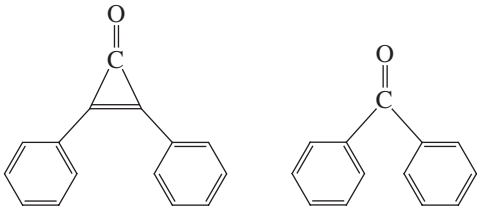
resonance contributors of the cycloheptatrienyl cation



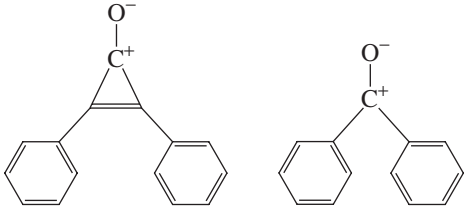
resonance hybrid

PROBLEM-SOLVING STRATEGY

Which of the following compounds has the greater dipole moment?



Before attempting to answer this kind of question, make sure that you know exactly what the question is asking. You know that the dipole moment of these compounds results from the unequal sharing of electrons by carbon and oxygen. Therefore, the more unequal the sharing, the greater is the dipole moment. So now the question becomes, which compound has a greater negative charge on its oxygen atom? Draw the structures with separated charges, and determine their relative stabilities. In the case of the compound on the left, the three-membered ring becomes aromatic when the charges are separated. In the case of the compound on the right, the structure with separated charges is not aromatic. Because being aromatic makes a compound more stable, the compound on the left has the greater dipole moment.



PROBLEM 9

Draw the resonance contributors of the cyclooctatrienyl dianion.

a. Which of the resonance contributors is the least stable?
b. Which of the resonance contributors makes the smallest contribution to the hybrid?

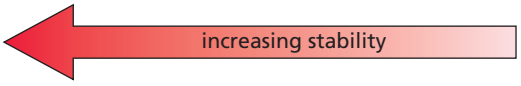
15.5 Antiaromaticity

Antiaromatic compounds are highly unstable.

An aromatic compound is *more stable* than an analogous cyclic compound with localized electrons. In contrast, an **antiaromatic** compound is *less stable* than an analogous cyclic compound with localized electrons. *Aromaticity is characterized by stability, whereas antiaromaticity is characterized by instability.*

relative stabilities

aromatic compound > cyclic compound with localized electrons > antiaromatic compound



A compound is classified as being antiaromatic if it fulfills the first criterion for aromaticity but does not fulfill the second criterion. In other words, it must be a planar, cyclic compound with an uninterrupted ring of p orbital-bearing atoms, and the π cloud must contain an *even* number of pairs of π electrons. Hückel would state that the π cloud must contain $4n$ π electrons, where n is any whole number—a mathematical way of saying that the cloud must contain an *even* number of pairs of π electrons.

Cyclobutadiene is a planar, cyclic molecule with two pairs of π electrons. Hence, it is expected to be antiaromatic and highly unstable. In fact, it is too unstable to be isolated, although it has been trapped at very cold temperatures. The cyclopentadienyl cation also has two pairs of π electrons, so we can conclude that it is antiaromatic and unstable.

cyclobutadiene

cyclopentadienyl cation

PROBLEM 10◆

a. Predict the relative pK_a values of cyclopropene and cyclopropane.
b. Which is more soluble in water, 3-bromocyclopropene or bromocyclopropane?

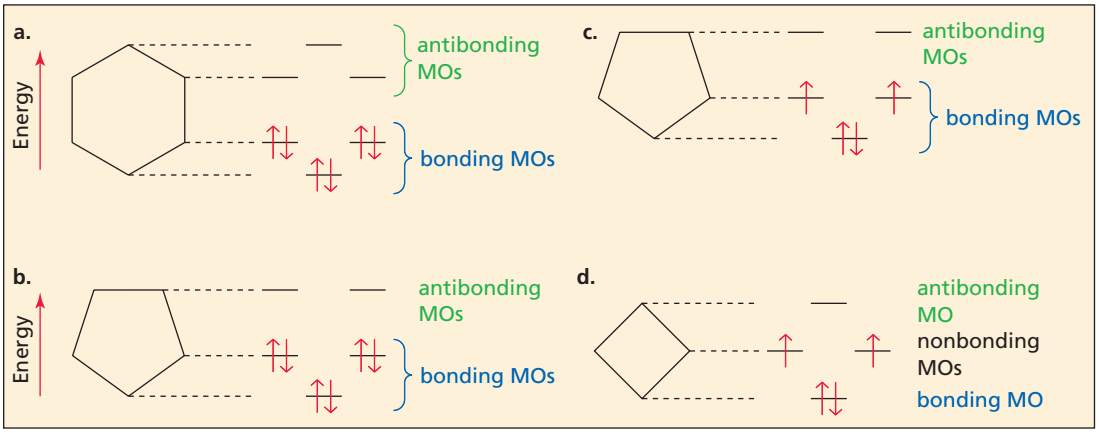
PROBLEM 11◆

Which of the compounds in Problem 2 are antiaromatic?

15.6 A Molecular Orbital Description of Aromaticity and Antiaromaticity

Why are planar molecules with uninterrupted cyclic π electron clouds highly stable (aromatic) if they have an odd number of pairs of π electrons and highly unstable (antiaromatic) if they have an even number of pairs of π electrons? To answer this question, we must turn to molecular orbital theory.

The relative energies of the π molecular orbitals of a planar molecule with an uninterrupted cyclic π electron cloud can be determined—without having to use any math—by first drawing the cyclic compound with one of its vertices pointed down. The relative energies of the π molecular orbitals correspond to the relative levels of the vertices (Figure 15.2). Molecular orbitals below the midpoint of the cyclic structure are bonding molecular orbitals, those above the midpoint are antibonding molecular orbitals, and any at the midpoint are nonbonding molecular orbitals. This scheme is sometimes called a Frost device (or a Frost circle) in honor of Arthur A. Frost, an



▲ Figure 15.2
The distribution of electrons in the π molecular orbitals of (a) benzene, (b) the cyclopentadienyl anion, (c) the cyclopentadienyl cation, and (d) cyclobutadiene. The relative energies of the π molecular orbitals in a cyclic compound correspond to the relative levels of the vertices. Molecular orbitals below the midpoint of the cyclic structure are bonding, those above the midpoint are antibonding, and those at the midpoint are nonbonding.

American scientist who devised this simple method. Notice that the number of π molecular orbitals is the same as the number of atoms in the ring because each ring atom contributes a *p* orbital. (Recall that orbitals are conserved; Section 7.11.)

The six π electrons of benzene occupy its three bonding π molecular orbitals, and the six π electrons of the cyclopentadienyl anion occupy *its* three bonding π molecular orbitals. Notice that there is always an odd number of bonding orbitals because one corresponds to the lowest vertex and the others come in degenerate pairs. This means that aromatic compounds—such as benzene and the cyclopentadienyl anion—with an odd number of pairs of π electrons have completely filled bonding orbitals and no electrons in either nonbonding or antibonding orbitals. This is what gives aromatic molecules their stability. (A more in-depth description of the molecular orbitals in benzene is given in Section 7.11.)

Tutorial:
Molecular orbital description of aromaticity

Aromatic compounds are stable because they have filled bonding π molecular orbitals.

Antiaromatic compounds have an even number of pairs of π electrons. Therefore, either they are unable to fill their bonding orbitals (cylopentadienyl cation) or they have a pair of π electrons left over after the bonding orbitals are filled (cyclobutadiene). Hund's rule requires that these two electrons go into two degenerate orbitals (Section 1.2). The unpaired electrons are responsible for the instability of antiaromatic molecules.

PROBLEM 12◆

How many bonding, nonbonding, and antibonding π molecular orbitals does cyclobutadiene have? In which molecular orbitals are the π electrons?

PROBLEM 13◆

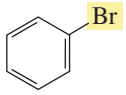
Can a radical be aromatic?

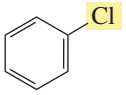
PROBLEM 14

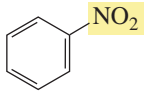
Following the instructions for drawing the π molecular orbital energy levels of the compounds shown in Figure 15.2, draw the π molecular orbital energy levels for the cycloheptatrienyl cation, the cycloheptatrienyl anion, and the cyclopropenyl cation. For each compound, show the distribution of the π electrons. Which of the compounds are aromatic? Which are antiaromatic?

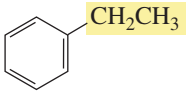
15.7 Nomenclature of Monosubstituted Benzenes

Some monosubstituted benzenes are named simply by stating the name of the substituent, followed by the word "benzene."

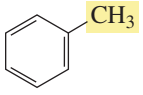

bromobenzene

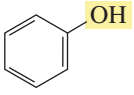

chlorobenzene

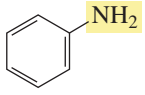

nitrobenzene
used as a solvent
in shoe polish

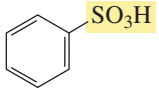

ethylbenzene

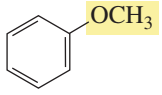
Some monosubstituted benzenes have names that incorporate the name of the substituent. Unfortunately, such names have to be memorized.

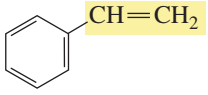

toluene

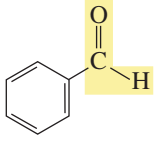

phenol

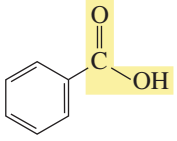

aniline

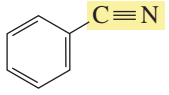

benzenesulfonic acid


anisole

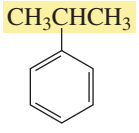

styrene

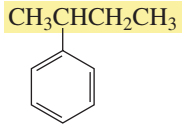

benzaldehyde

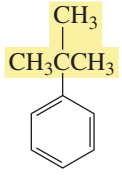

benzoic acid

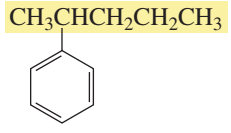

benzonitrile

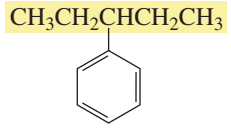
With the exception of toluene, benzene rings with an alkyl substituent are named as alkyl-substituted benzenes or as phenyl-substituted alkanes.


isopropylbenzene
cumene

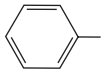

sec-butylbenzene

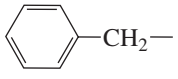

tert-butylbenzene

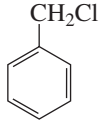

2-phenylpentane

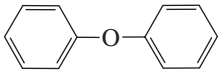

3-phenylpentane

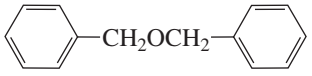
When a benzene ring is a substituent, it is called a **phenyl group**. A benzene ring with a methylene group is called a **benzyl group**. The phenyl group gets its name from "pheno," the name that was rejected for benzene (Section 15.0).


a phenyl group

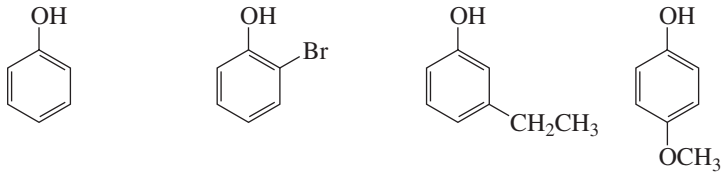

a benzyl group


chloromethylbenzene
benzyl chloride


diphenyl ether


dibenzyl ether

An aryl group (Ar) is the general term for either a phenyl group or a substituted phenyl group, just as an alkyl group (R) is the general term for a group derived from an alkane. In other words, ArOH could be used to designate any of the following phenols:



THE TOXICITY OF BENZENE

Although benzene has been widely used in chemical synthesis and has been frequently used as a solvent, it is toxic. Its major toxic effect is on the central nervous system and on bone marrow. Chronic exposure to benzene causes leukemia and aplastic anemia. A higher-than-average incidence of leukemia has been found in industrial workers with long-term exposure to as little as 1 ppm benzene in the atmosphere. Toluene has replaced benzene as a solvent because, although it is a central nervous system depressant like benzene, it does not cause leukemia or aplastic anemia. "Glue sniffers" seek the narcotic central nervous system effects of solvents such as toluene. This can be a highly dangerous activity.

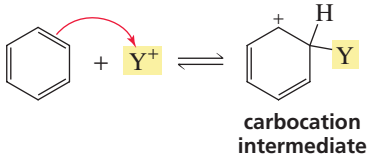
PROBLEM 15◆

Draw the structure of each of the following compounds:

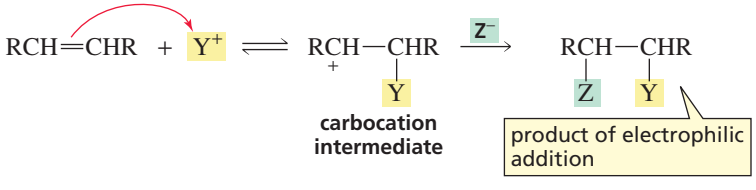
a. 2-phenylhexane
b. benzyl alcohol
c. 3-benzylpentane
d. bromomethylbenzene

15.8 How Benzene Reacts

As a consequence of the π electrons above and below the plane of its ring, benzene is a nucleophile. It will, therefore, react with an electrophile (Y^+). When an electrophile attaches itself to a benzene ring, a carbocation intermediate is formed.



This should remind you of the first step in an electrophilic addition reaction of an alkene: A nucleophilic alkene reacts with an electrophile, thereby forming a carbocation intermediate (Section 3.6). In the second step of an electrophilic addition reaction, the carbocation reacts with a nucleophile (Z^-) to form an addition product.



If the carbocation intermediate formed from the reaction of benzene with an electrophile were to react similarly with a nucleophile (depicted as event *b* in Figure 15.3), the addition product would not be aromatic. If, however, the carbocation loses a proton from the site of electrophilic attack (depicted as event *a* in Figure 15.3), the aromaticity of the benzene ring is restored. Because the aromatic product is much more stable than the nonaromatic addition product, the overall reaction is an electrophilic substitution reaction rather than an electrophilic addition reaction. In the substitution reaction, an electrophile substitutes for one of the hydrogens attached to the benzene ring.

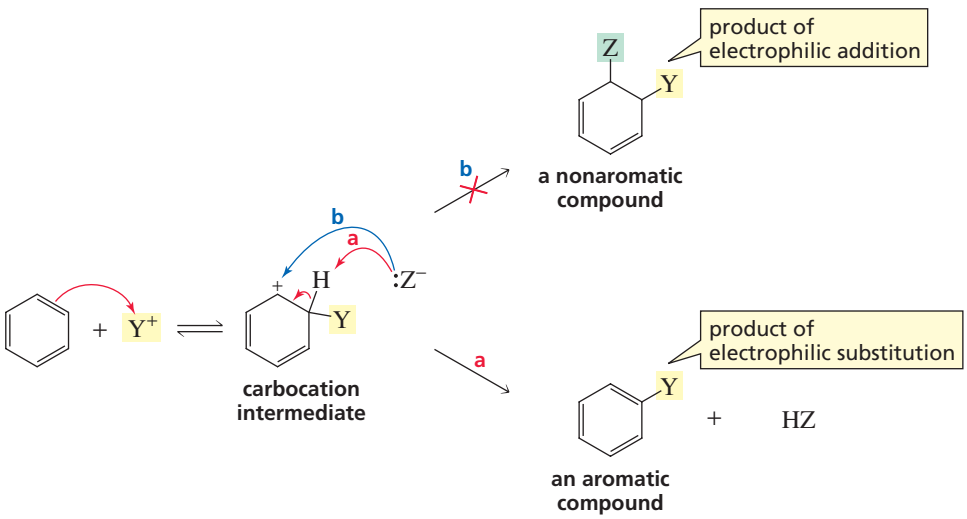


Figure 15.3 ▶
Reaction of benzene with an electrophile. Because the aromatic product is more stable, the reaction proceeds as (a) an electrophilic substitution reaction rather than (b) an electrophilic addition reaction.

The reaction coordinate diagram in Figure 15.4 shows that the reaction of *benzene* to form a *substituted benzene* has a ΔG° close to zero. The reaction of *benzene* to form the much less stable *nonaromatic addition product* would have been a highly endergonic reaction. Consequently, benzene undergoes *electrophilic substitution reactions* that preserve aromaticity, rather than *electrophilic addition reactions* (the reactions characteristic of alkenes), which would destroy aromaticity.

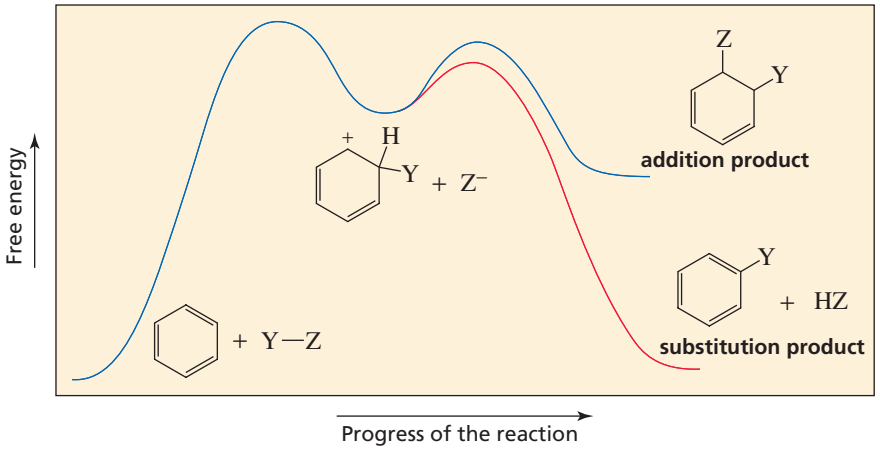


Figure 15.4 ▶
Reaction coordinate diagrams for electrophilic substitution of benzene and electrophilic addition to benzene.

PROBLEM 16

If electrophilic addition to benzene is an endergonic reaction overall, how can electrophilic addition to an alkene be an exergonic reaction overall?

15.9 General Mechanism for Electrophilic Aromatic Substitution Reactions

Because electrophilic substitution of benzene involves the reaction of an electrophile with an aromatic compound, it is more precisely called an electrophilic aromatic substitution reaction. In an **electrophilic aromatic substitution reaction**, an electrophile substitutes for a hydrogen of an aromatic compound.

an electrophilic aromatic substitution reaction

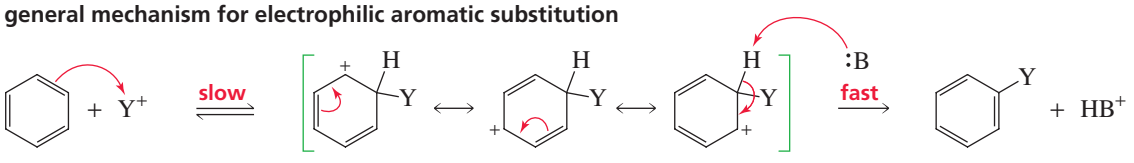
The following are the five most common electrophilic aromatic substitution reactions:

1. **Halogenation**: A bromine (Br), a chlorine (Cl), or an iodine (I) substitutes for a hydrogen.
2. **Nitration**: A nitro (NO_2) group substitutes for a hydrogen.
3. **Sulfonation**: A sulfonic acid (SO_3H) group substitutes for a hydrogen.
4. **Friedel–Crafts acylation**: An acyl (RC═O) group substitutes for a hydrogen.
5. **Friedel–Crafts alkylation**: an alkyl (R) group substitutes for a hydrogen.

All of these electrophilic aromatic substitution reactions take place by the same two-step mechanism. In the first step, benzene reacts with an electrophile (Y^+), forming a carbocation intermediate. The structure of the carbocation intermediate can be approximated by three resonance contributors. In the second step of the reaction, a base in the reaction mixture pulls off a proton from the carbocation intermediate, and the electrons that held the proton move into the ring to reestablish its aromaticity. Notice that *the proton is always removed from the carbon that has formed the new bond with the electrophile*.

In an electrophilic aromatic substitution reaction, an electrophile (Y^+) is put on a ring carbon, and the H^+ comes off the same ring carbon.

general mechanism for electrophilic aromatic substitution



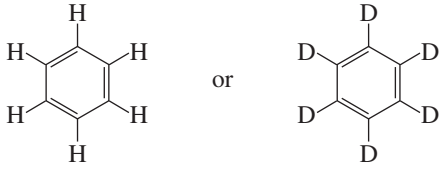
The first step is relatively slow and endergonic because an aromatic compound is being converted into a much less stable nonaromatic intermediate (Figure 15.4). The second step is fast and strongly exergonic because this step restores the stability-enhancing aromaticity.

Tutorial: Electrophilic aromatic substitution

We will look at each of these five electrophilic aromatic substitution reactions individually. As you study them, notice that they differ only in how the electrophile (Y^+) needed to start the reaction is generated. Once the electrophile is formed, all five reactions follow the same two-step mechanism for electrophilic aromatic substitution.

PROBLEM 17◆

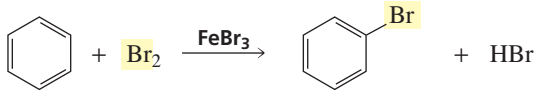
Which compound will undergo an electrophilic aromatic substitution reaction more rapidly, benzene or hexadeuteriobenzene?



15.10 Halogenation of Benzene

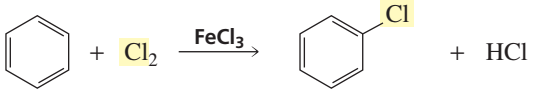
The bromination or chlorination of benzene requires a Lewis acid such as ferric bromide or ferric chloride. Recall that a *Lewis acid* is a compound that accepts a share in a pair of electrons (Section 1.21).

bromination



bromobenzene

chlorination

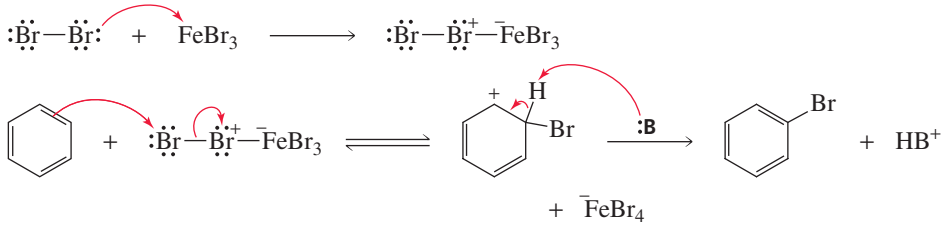


chlorobenzene

Movie: Bromination of benzene

In the first step of the bromination reaction, bromine donates a lone pair to the Lewis acid. This weakens the Br—Br bond, thereby providing the electrophile necessary for electrophilic aromatic substitution.

mechanism for bromination

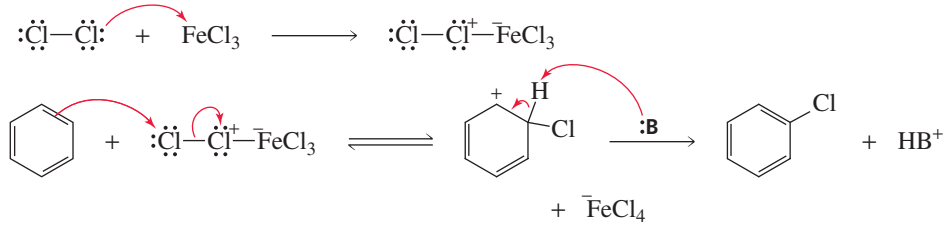


To make the mechanisms easier to understand, only one of the three resonance contributors of the carbocation intermediate is shown in this and subsequent illustrations. Bear in mind, however, that each carbocation intermediate actually has the three resonance contributors shown in Section 15.9. In the last step of the reaction, a base (:B) from the reaction mixture removes a proton from the carbocation intermediate. The following equation shows that the catalyst is regenerated:

$$\text{FeBr}_4^- + \text{HB}^+ \longrightarrow \text{HBr} + \text{FeBr}_3 + \text{:B}$$

Chlorination of benzene occurs by the same mechanism as bromination.

mechanism for chlorination



Ferric bromide and ferric chloride react readily with moisture in the air during handling, which inactivates them as catalysts. Therefore, instead of using the actual salt, ferric bromide or ferric chloride is generated in situ (in the reaction mixture) by adding iron filings and bromine or chlorine to the reaction mixture. Therefore, the halogen in the Lewis acid is the same as the reagent halogen.

$$2\ Fe + 3\ Br_2 \longrightarrow 2\ FeBr_3$$

$$2\ Fe + 3\ Cl_2 \longrightarrow 2\ FeCl_3$$

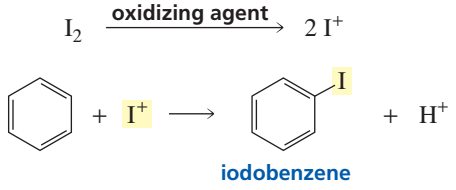
Unlike the reaction of benzene with Br_2 or Cl_2, the reaction of an alkene with Br_2 or Cl_2 does not require a Lewis acid (Section 4.7). An alkene is more reactive than benzene because an alkene has a smaller activation energy, since carbocation formation is not accompanied by a loss of aromaticity. As a result, the Br—Br or Cl—Cl bond does not have to be weakened to form a better electrophile.

PROBLEM 18

Why does hydration inactivate $FeBr_3$?

Electrophilic iodine (I^+) is obtained by treating I_2 with an oxidizing agent such as nitric acid.

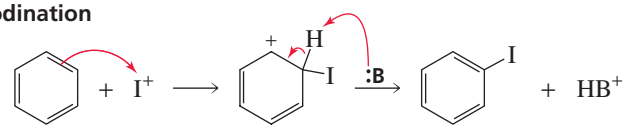
iodination



iodobenzene

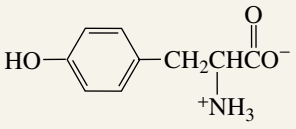
Once the electrophile is formed, iodination of benzene occurs by the same mechanism as bromination and chlorination.

mechanism for iodination

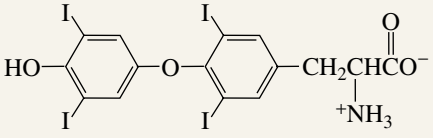


THYROXINE

Thyroxine is a hormone that regulates the metabolic rate, causing an increase in the rate at which fats, carbohydrates, and proteins are metabolized. Humans obtain thyroxine from tyrosine (an amino acid) and iodine. We get iodine primarily from the iodized salt in our diet. An enzyme called iodoperoxidase converts the I^- we ingest to I^+, the electrophile needed to place an iodo substituent on the benzene ring. Low thyroxine levels can be corrected by hormone supplements. Chronically low levels of thyroxine cause enlargement of the thyroid gland, a condition known as goiter.



tyrosine

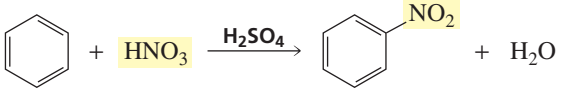


thyroxine

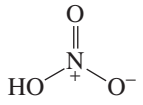
15.11 Nitration of Benzene

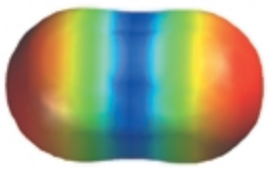
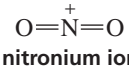
Nitration of benzene with nitric acid requires sulfuric acid as a catalyst.

nitration



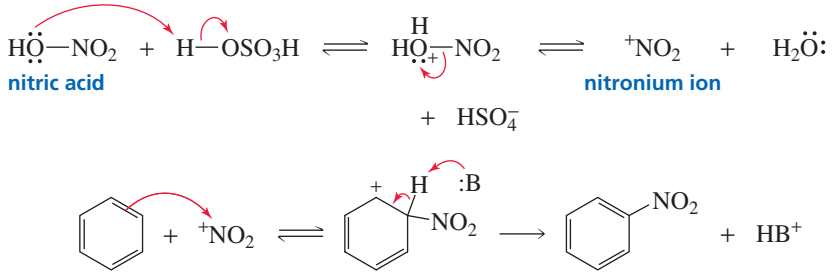
nitrobenzene


nitric acid



nitronium ion

To generate the necessary electrophile, sulfuric acid protonates nitric acid. Loss of water from protonated nitric acid forms a nitronium ion, the electrophile required for nitration. Remember that any base (:B) present in the reaction mixture (H_2O, HSO_4^-, solvent) can remove the proton in the second step of the aromatic substitution reaction.

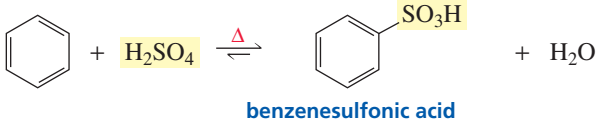
mechanism for nitration



15.12 Sulfonation of Benzene

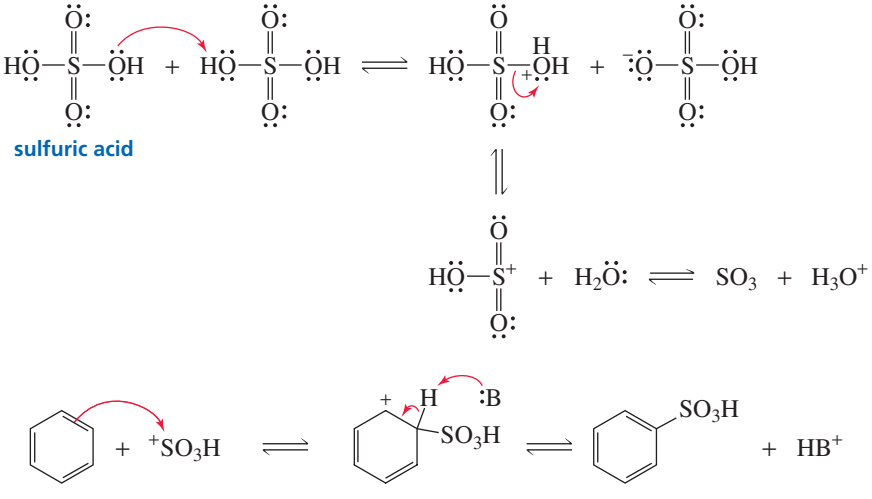
Fuming sulfuric acid (a solution of SO_3 in sulfuric acid) or concentrated sulfuric acid is used to sulfonate aromatic rings.

sulfonation

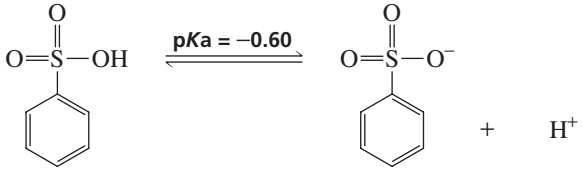


As the following mechanism shows, a substantial amount of electrophilic sulfur trioxide (SO_3) is generated when concentrated sulfuric acid is heated, as a result of the $^+SO_3H$ electrophile losing a proton. Take a minute to note the similarities in the mechanisms for forming the $^+SO_3H$ electrophile for sulfonation and the $^+NO_2$ electrophile for nitration.

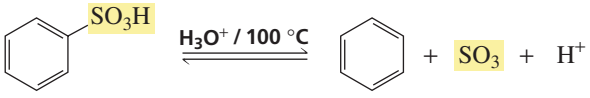
mechanism for sulfonation



A sulfonic acid is a strong acid because of the three electron-withdrawing oxygen atoms and the stability of its conjugate base—the electrons left behind when a proton is lost are shared by three oxygen atoms (Section 1.19).

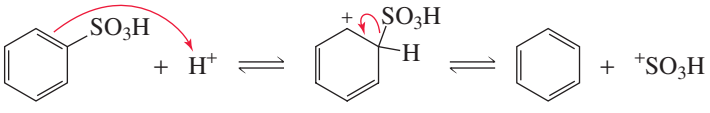


Sulfonation of benzene is a reversible reaction. If benzenesulfonic acid is heated in dilute acid, the reaction proceeds in the reverse direction.



The **principle of microscopic reversibility** applies to all reactions. It states that the mechanism of a reaction in the reverse direction must retrace each step of the mechanism in the forward direction in microscopic detail. This means that the forward and reverse reactions must have the same intermediates and that the rate-determining "energy hill" must be the same in both directions. For example, sulfonation is described by the reaction coordinate diagram in Figure 15.5, going from left to right. Therefore, desulfonation is described by the same reaction coordinate diagram going from right to left. In sulfonation, the rate-determining step is nucleophilic attack of benzene on the $^{+}SO_3H$ ion. In desulfonation, the rate-limiting step is loss of the $^{+}SO_3H$ ion from the benzene ring. An example of the usefulness of desulfonation to synthetic chemists is given in Chapter 16, Problem 19.

mechanism for desulfonation



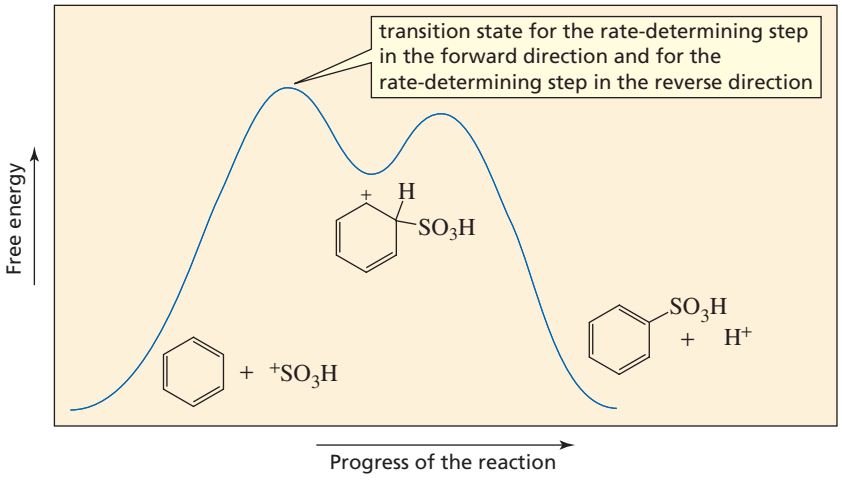
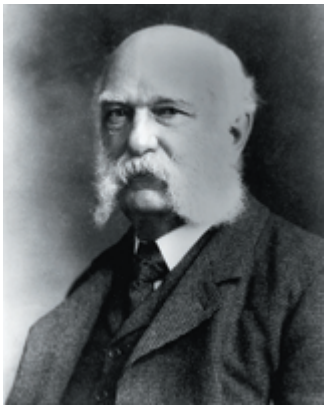

transition state for the rate-determining step in the forward direction and for the rate-determining step in the reverse direction
Free energy
Progress of the reaction

Figure 15.5
Reaction coordinate diagram for the sulfonation of benzene (left to right) and the desulfonation of benzenesulfonic acid (right to left).

PROBLEM 19

The reaction coordinate diagram in Figure 15.5 shows that the rate-determining step for sulfonation is the slower of the two steps, whereas the rate-determining step for desulfonation is the faster of the two steps. Explain how the faster step can be the rate-determining step.

Charles Friedel (1832–1899) *was born in Strasbourg, France. He was a professor of chemistry and director of research at the Sorbonne. At one point, his interest in mineralogy led him to attempt to make synthetic diamonds. He met James Crafts when they both were doing research at L'Ecole de Médicine in Paris. They collaborated scientifically for most of their lives, discovering the Friedel–Crafts reactions in Friedel's laboratory in 1877.*



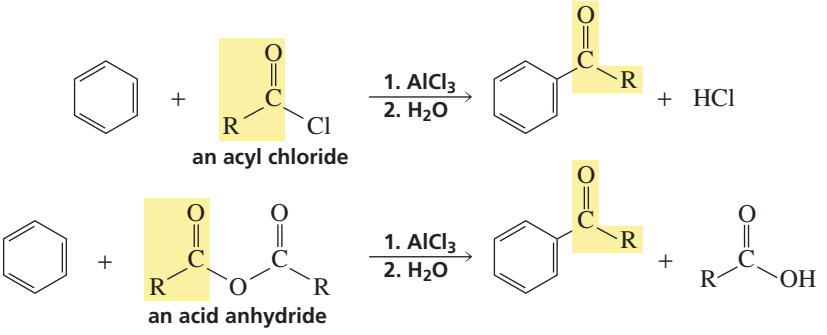
James Mason Crafts (1839–1917) *was born in Boston, the son a of woolen-goods manufacturer. He graduated from Harvard in 1858 and was a professor of chemistry at Cornell University and the Massachusetts Institute of Technology. He was president of MIT from 1897 to 1900, when he was forced to retire because of chronic poor health.*

15.13 Friedel–Crafts Acylation of Benzene

Two electrophilic substitution reactions bear the names of chemists Charles Friedel and James Crafts. *Friedel–Crafts acylation* places an acyl group on a benzene ring, and *Friedel–Crafts alkylation* places an alkyl group on a benzene ring.

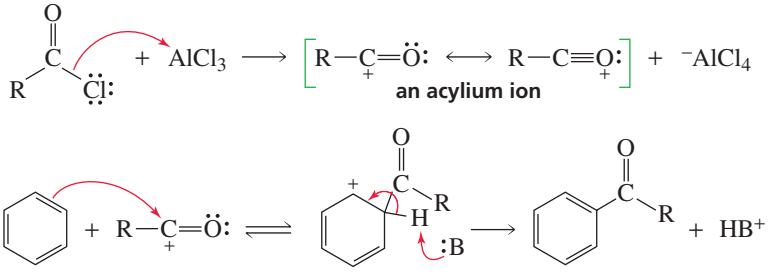
Either an acyl halide or an acid anhydride can be used for Friedel–Crafts acylation.

Friedel–Crafts acylation

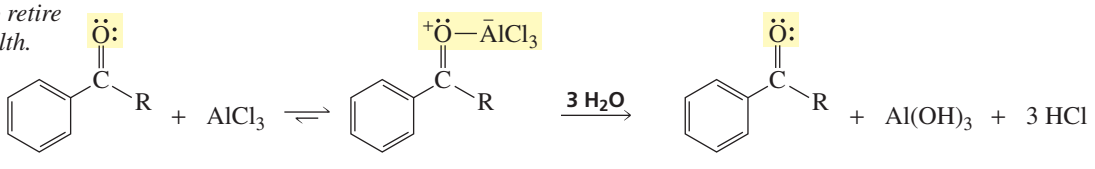


An acylium ion is the electrophile required for a Friedel–Crafts acylation reaction. This ion is formed by the reaction of an acyl chloride or an acid anhydride with $AlCl_3$, a Lewis acid.

mechanism for Friedel–Crafts acylation



Because the product of a Friedel–Crafts acylation reaction contains a carbonyl group that can complex with $AlCl_3$, Friedel–Crafts acylation reactions must be carried out with more than one equivalent of $AlCl_3$. When the reaction is over, water is added to the reaction mixture to liberate the product from the complex.

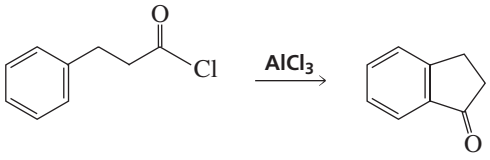


PROBLEM 20

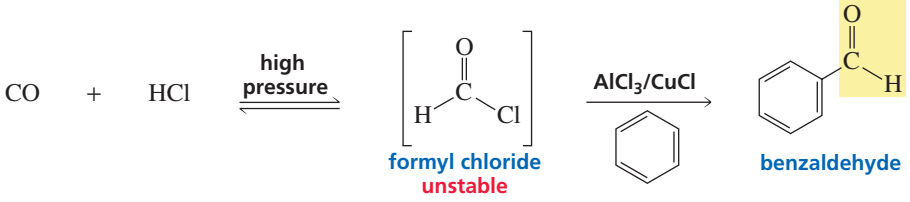
Show the mechanism for the generation of the acylium ion if an acid anhydride is used instead of an acyl chloride in a Friedel–Crafts acylation reaction.

PROBLEM 21

Propose a mechanism for the following reaction:



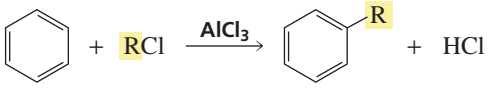
The synthesis of benzaldehyde from benzene poses a problem because formyl chloride, the acyl halide required for the reaction, is unstable and cannot be purchased. Formyl chloride can be prepared, however, by means of the **Gatterman–Koch** formylation **reaction**. This reaction uses a high-pressure mixture of carbon monoxide and HCl to generate formyl chloride, along with an aluminum chloride–cuprous chloride catalyst to carry out the acylation reaction.



15.14 Friedel–Crafts Alkylation of Benzene

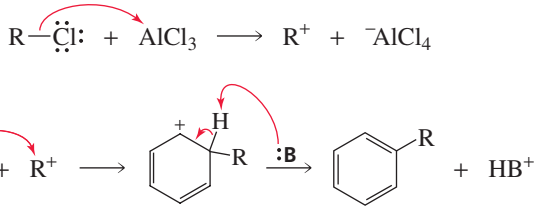
The Friedel–Crafts alkylation reaction substitutes an alkyl group for a hydrogen.

Friedel–Crafts alkylation



In the first step of the reaction, a carbocation is formed from the reaction of an alkyl halide with $AlCl_3$. Alkyl fluorides, alkyl chlorides, alkyl bromides, and alkyl iodides can all be used. Vinyl halides and aryl halides cannot be used because their carbocations are too unstable to be formed (Section 10.8).

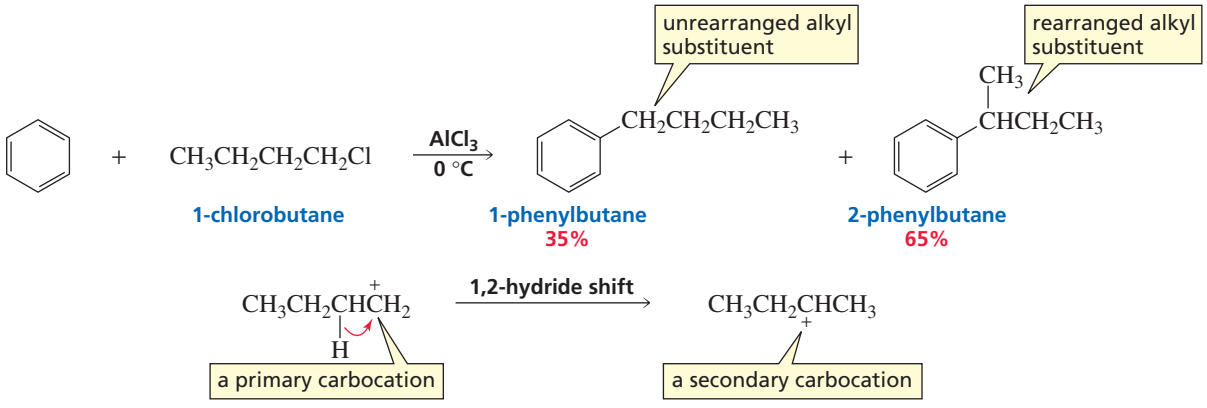
mechanism for Friedel–Crafts alkylation



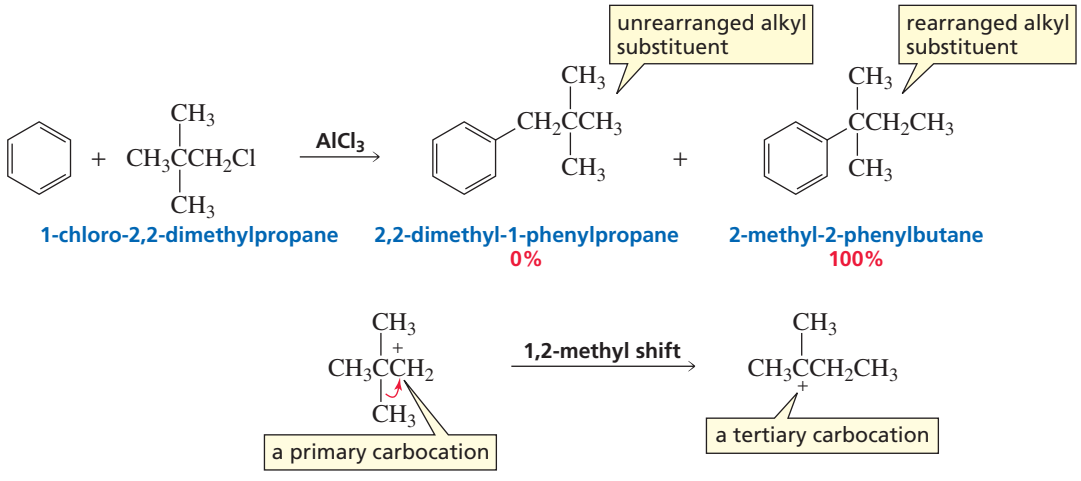
In Section 16.3, we will see that an alkyl-substituted benzene is more reactive than benzene. Therefore, to prevent further alkylation of the alkyl-substituted benzene, a large excess of benzene is used in Friedel–Crafts alkylation reactions. This approach ensures that the electrophile is more likely to encounter a molecule of benzene than a molecule of alkyl-substituted benzene.

Recall that a carbocation will rearrange if rearrangement leads to a more stable carbocation (Section 4.6). When the carbocation can rearrange in a Friedel–Crafts alkylation reaction, the major product will be the product with the rearranged alkyl group on

the benzene ring. The relative amounts of rearranged and unrearranged product depend on the increase in carbocation stability achieved as a result of the rearrangement. For example, when benzene reacts with 1-chlorobutane, a primary carbocation rearranges to a secondary carbocation, and 60–80% of the product (the actual percentage depends on the reaction conditions) is the rearranged product.

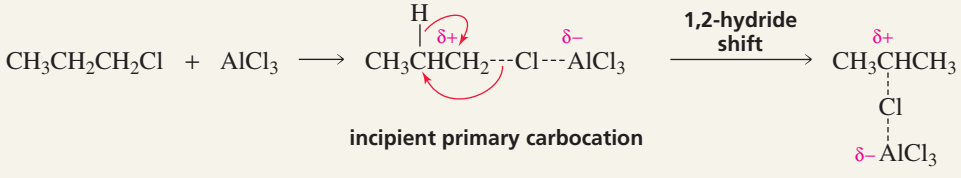


When benzene reacts with 1-chloro-2,2-dimethylpropane, a primary carbocation rearranges to a tertiary carbocation. Thus, there is a greater increase in carbocation stability and, therefore, a greater amount of rearranged product—100% of the product (under all reaction conditions) has the rearranged alkyl substituent.



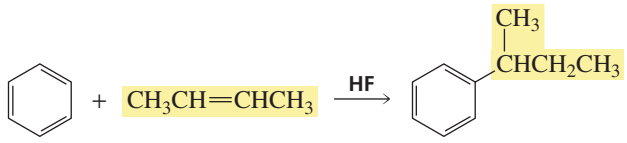
INCIPIENT PRIMARY CARBOCATIONS

For simplicity, we have shown the formation of a primary carbocation in the two preceding reactions. However, as we saw in Section 10.5, primary carbocations are too unstable to be formed in solution. The fact is that a true primary carbocation is never formed in a Friedel–Crafts alkylation reaction. Instead, the carbocation remains complexed with the Lewis acid—it is called an "incipient" carbocation. A carbocation rearrangement occurs because the incipient carbocation has sufficient carbocation character to permit the rearrangement.



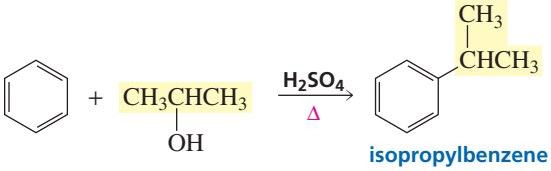
In addition to reacting with carbocations generated from alkyl halides, benzene can react with carbocations generated from the reaction of an alkene (Section 4.1) or an alcohol (Section 12.1) with an acid.

alkylation of benzene by an alkene



sec-butylbenzene

alkylation of benzene by an alcohol



isopropylbenzene
cumene

PROBLEM 22

Show the mechanism for alkylation of benzene by an alkene.

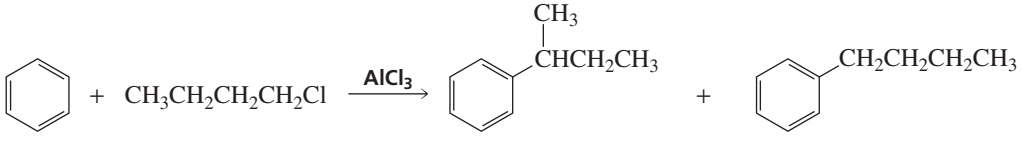
PROBLEM 23◆

What would be the major product of a Friedel–Crafts alkylation reaction using the following alkyl halides?

a. CH_3CH_2Cl
b. $CH_3CH_2CH_2Cl$
c. $CH_3CH_2CH(Cl)CH_3$
d. $(CH_3)_3CCH_2Cl$
e. $(CH_3)_2CHCH_2Cl$
f. $CH_2{=}CHCH_2Cl$

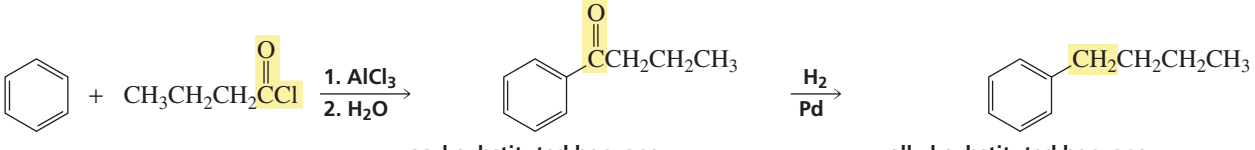
15.15 Alkylation of Benzene by Acylation–Reduction

It is not possible to obtain a good yield of an alkylbenzene containing a straight-chain alkyl group via a Friedel–Crafts alkylation reaction, because the incipient primary carbocation will rearrange to a more stable carbocation.



major product minor product

Acylium ions, however, do not rearrange. Consequently, a straight-chain alkyl group can be placed on a benzene ring by means of a Friedel–Crafts acylation reaction, followed by reduction of the carbonyl group to a methylene group. It is called a reduction reaction because the two C—O bonds are replaced by two C—H bonds (Section 4.8). Only a ketone carbonyl group that is adjacent to a benzene ring can be reduced to a methylene group by catalytic hydrogenation (H_2/Pd) .



acyl-substituted benzene alkyl-substituted benzene

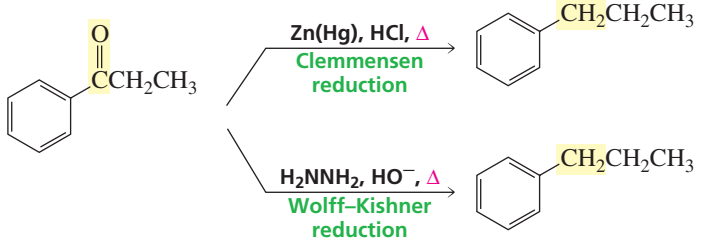
E. C. Clemmensen (1876–1941) *was born in Denmark and received a Ph.D. from the University of Copenhagen. He was a scientist at Clemmensen Corp. in Newark, New York.*

Ludwig Wolff (1857–1919) *was born in Germany. He received a Ph.D. from the University of Strasbourg. He was a professor at the University of Jena in Germany.*

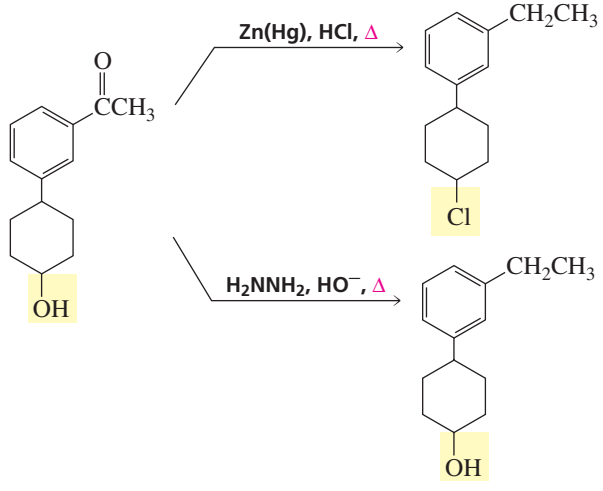
N. M. Kishner (1867–1935) *was born in Moscow. He received a Ph.D. from the University of Moscow under the direction of Markovnikov. He was a professor at the University of Tomsk and later at the University of Moscow.*

Besides avoiding carbocation rearrangements, another advantage of preparing alkyl-substituted benzenes by acylation–reduction rather than by direct alkylation is that a large excess of benzene does not have to be used (Section 15.14). Unlike alkyl-substituted benzenes, which are more reactive than benzene (Section 16.3), acyl-substituted benzenes are less reactive than benzene, so they will not undergo additional Friedel–Crafts reactions.

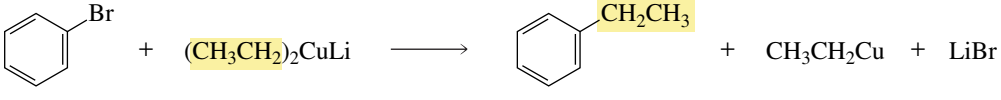
There are more general methods available to reduce a ketone carbonyl group to a methylene group—methods that reduce all ketone carbonyl groups, not just those that are adjacent to benzene rings. Two of the most effective are the Clemmensen reduction and the Wolff–Kishner reduction. The **Clemmensen reduction** uses an acidic solution of zinc dissolved in mercury as the reducing reagent. The **Wolff–Kishner reduction** employs hydrazine (H_2NNH_2) under basic conditions. The mechanism of the Wolff–Kishner reduction is shown in Section 18.6.



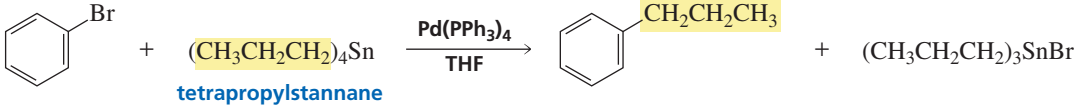
At this point, you may wonder why it is necessary to have more than one way to carry out the same reaction. Alternative methods are useful when there is another functional group in the molecule that could react with the reagents you are using to carry out the desired reaction. For example, heating the following compound with HCl (as required by the Clemmensen reduction) would cause the alcohol to undergo substitution (Section 11.1). Under the basic conditions of the Wolff–Kishner reduction, however, the alcohol group would remain unchanged.



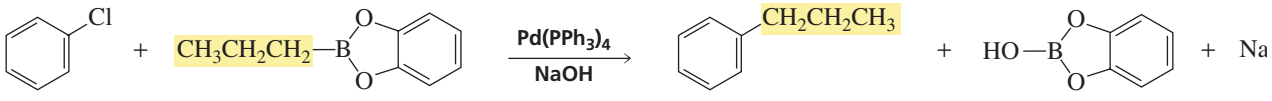
Alkylbenzenes with straight-chain alkyl groups can also be prepared by means of the coupling reactions you saw in Section 12.12. One of the alkyl groups of a Gilman reagent can replace the halogen of an aryl halide.



The **Stille reaction** couples an aryl halide with a stannane.

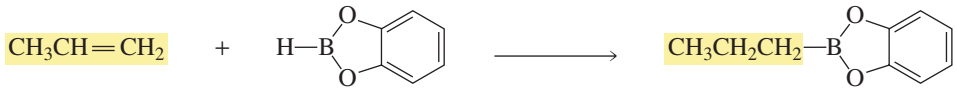


The **Suzuki reaction** couples an aryl halide with an organoborane.



an organoborane — propylbenzene

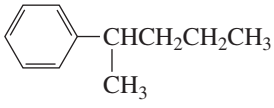
The required organoborane is obtained from the reaction of an alkene with catecholborane. Because alkenes are readily available, this method can be used to prepare a wide variety of alkyl benzenes.

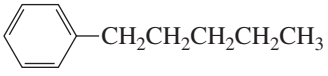


catecholborane

PROBLEM 24

Describe how the following compounds could be prepared from benzene:

a. 

b. 

Summary

To be classified as **aromatic**, a compound must have an uninterrupted cyclic cloud of π electrons that contains an *odd number of pairs* of π electrons. An **antiaromatic** compound has an uninterrupted cyclic cloud of π electrons with an *even number of pairs* of π electrons. Molecular orbital theory shows that aromatic compounds are stable because their bonding orbitals are completely filled, with no electrons in either nonbonding or antibonding orbitals; in contrast, antiaromatic compounds are unstable because they either are unable to fill their bonding orbitals or they have a pair of π electrons left over after the bonding orbitals are filled. As a result of their aromaticity, the cyclopentadienyl anion and the cycloheptatrienyl cation are unusually stable.

An **annulene** is a monocyclic hydrocarbon with alternating single and double bonds. A **heterocyclic compound** is a cyclic compound in which one or more of the ring atoms is a **heteroatom**—an atom other than carbon. Pyridine, pyrrole, furan, and thiophene are aromatic heterocyclic compounds.

Benzene's aromaticity causes it to undergo **electrophilic aromatic substitution reactions**. The electrophilic addition reactions characteristic of alkenes and dienes would lead to much less stable nonaromatic addition products. The most common electrophilic aromatic substitution reactions are halogenation, nitration, sulfonation, and Friedel–Crafts acylation and alkylation. Once the electrophile is generated, all electrophilic aromatic substitution reactions take place by the same two-step mechanism: (1) The aromatic compound reacts with an electrophile, forming a carbocation intermediate; and (2) a base pulls off a proton from the carbon that formed the bond with the electrophile. The first step is relatively slow and endergonic because an aromatic compound is being converted into a much less stable nonaromatic intermediate; the second step is fast and strongly exergonic because the stability-enhancing aromaticity is being restored.

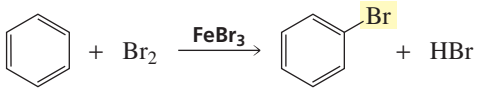
Some monosubstituted benzenes are named as substituted benzenes (e.g., bromobenzene, nitrobenzene); some have names that incorporate the name of the substituent (e.g., toluene, phenol, aniline). Bromination or chlorination requires a Lewis acid catalyst; iodination requires an oxidizing agent. **Nitration** with nitric acid requires sulfuric acid as a catalyst. Either an acyl halide or an acid anhydride can be used for **Friedel–Crafts acylation**, a reaction that places an acyl group on a benzene ring. If the carbocation formed from the alkyl halide used in a **Friedel–Crafts alkylation** reaction can rearrange, the major product will be the product with the rearranged alkyl group. A straight-chain alkyl group can be placed on a benzene ring via a Friedel–Crafts acylation reaction, followed by reduction of the carbonyl group by catalytic hydrogenation, a **Clemmensen reduction**, or a **Wolff–Kishner reduction**. Alkylbenzenes with straight-chain alkyl groups can also be prepared by means of coupling reactions.

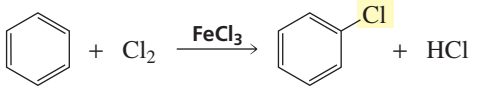
A benzene ring can be sulfonated with fuming or concentrated sulfuric acid. **Sulfonation** is a reversible reaction; heating benzenesulfonic acid in dilute acid removes the sulfonic acid group. The **principle of microscopic reversibility** states that the mechanism of a reaction in the reverse direction must retrace each step of the mechanism in the forward direction in microscopic detail.

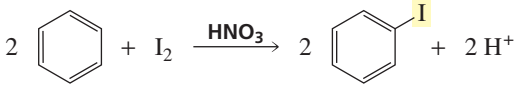
Summary of Reactions

1. Electrophilic aromatic substitution reactions:

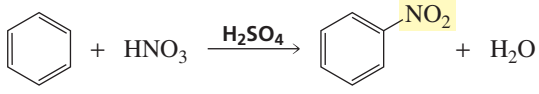
a. Halogenation (Section 15.10)

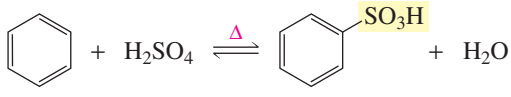




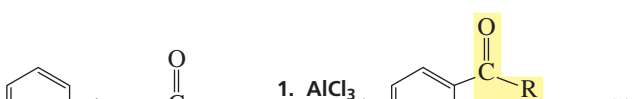


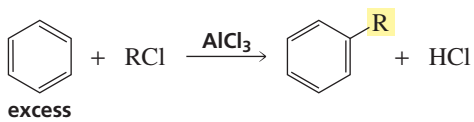
b. Nitration, sulfonation, and desulfonation (Sections 15.11 and 15.12)



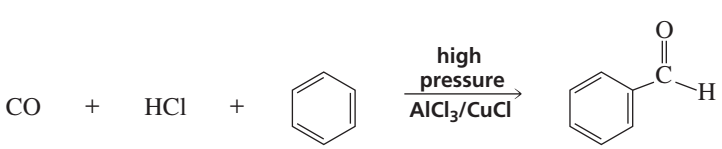


c. Friedel–Crafts acylation and alkylation (Sections 15.13 and 15.14)

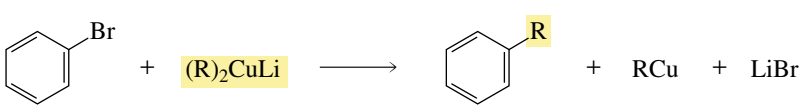




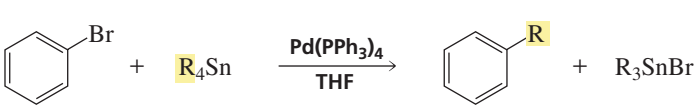
d. Formation of benzaldehyde via a Gatterman–Koch reaction (Section 15.13)



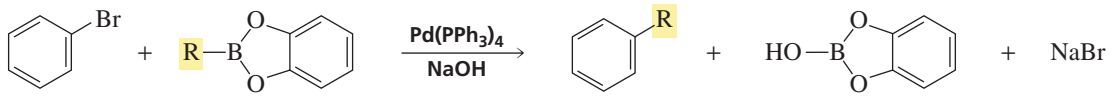
e. Alkylation with a Gilman reagent (15.15)



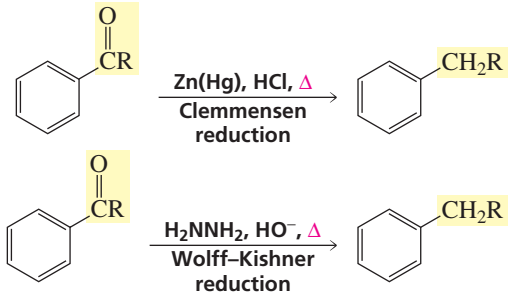
f. Alkylation via a Stille reaction (Section 15.15)



g. Alkylation via a Suzuki reaction (Section 15.15)



2. Clemmensen reduction and Wolff–Kishner reduction (Section 15.15)

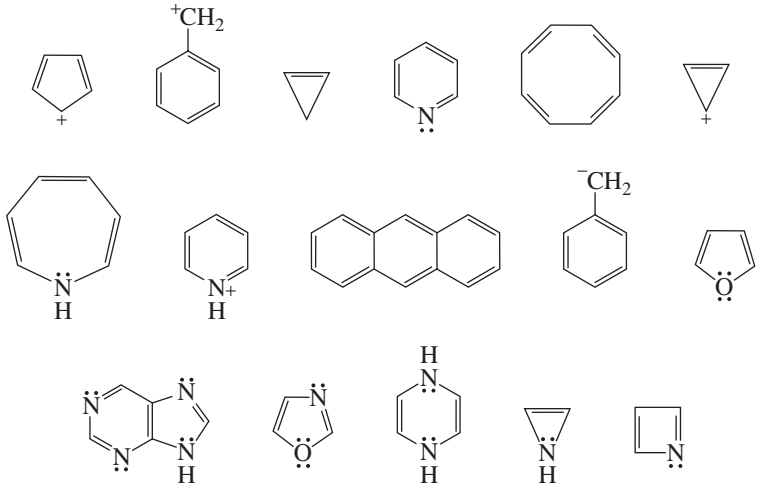


Key Terms

aliphatic (p. 594)
annulene (p. 595)
antiaromatic (p. 602)
aromatic (p. 595)
benzyl group (p. 604)
Clemmensen reduction (p. 616)
electrophilic aromatic substitution reaction (p. 607)
Friedel–Crafts acylation (p. 607)
Friedel–Crafts alkylation (p. 607)
Gatterman–Koch reaction (p. 613)
halogenation (p. 607)
heteroatom (p. 598)
heterocyclic compound (p. 598)
Hückel's rule, or the $4n + 2$ rule (p. 595)
nitration (p. 607)
phenyl group (p. 604)
principle of microscopic reversibility (p. 611)
Stille reaction (p. 616)
sulfonation (p. 607)
Suzuki reaction (p. 617)
Wolff–Kishner reduction (p. 616)

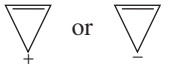
Problems

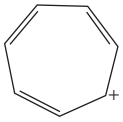
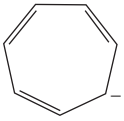
25. Which of the following compounds are aromatic? Are any antiaromatic? (*Hint:* If possible, a ring will be nonplanar to avoid being antiaromatic.)



26. Give the product of the reaction of excess benzene with each of the following reagents:
    a. isobutyl chloride + $AlCl_3$
    b. propene + HF
    c. neopentyl chloride + $AlCl_3$
    d. dichloromethane + $AlCl_3$

27. Which ion in each of the following pairs is more stable?

a.  or

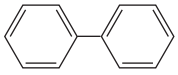
b.  or 

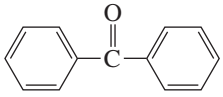
c. or

d. or

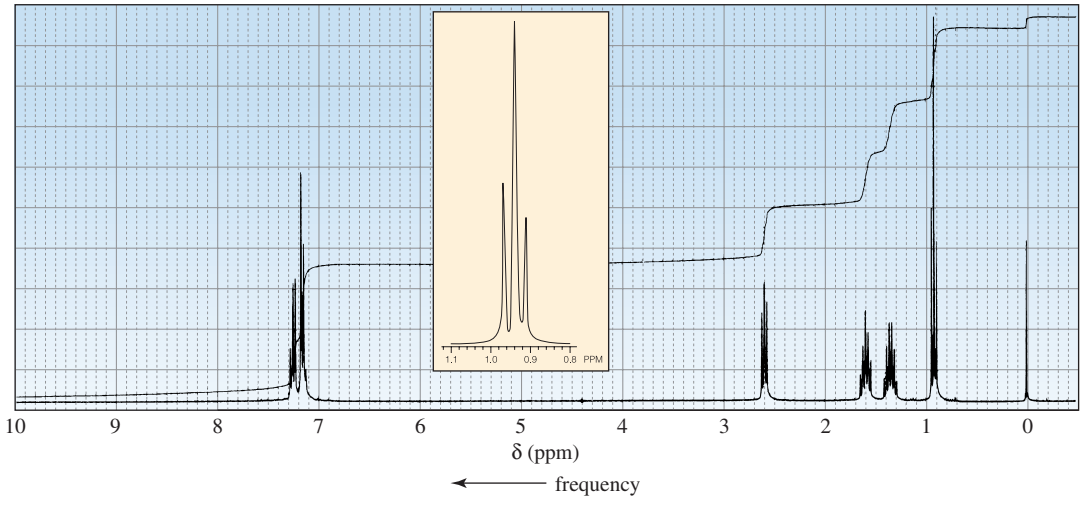
28. Which can lose a proton more readily, a methyl group bonded to cyclohexane or a methyl group bonded to benzene?

29. How could you prepare the following compounds with benzene as one of the starting materials?

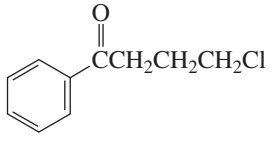
a. 

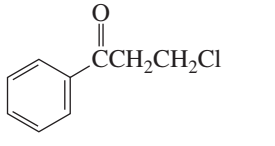
b. 

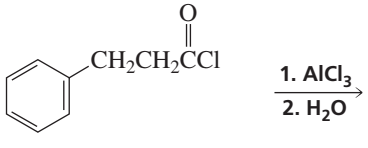
30. Benzene underwent a Friedel–Crafts acylation reaction followed by a Clemmensen reduction. The product gave the following ^{1}H NMR spectrum. What acyl chloride was used in the Friedel–Crafts acylation reaction?

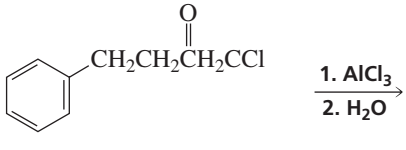


31. Give the products of the following reactions:

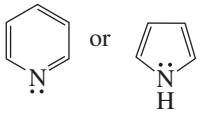
a. 

b. 

c. 

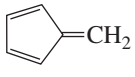
d. 

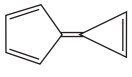
32. Which compound in each of the following pairs is a stronger base? Why?

a. 

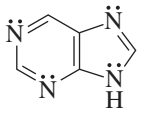
b. $CH_3\overset{\overset{NH_2}{|}}{C}HCH_3$ or $CH_3\overset{\overset{NH}{\|}}{C}NH_2$

33. a. In what direction is the dipole moment in fulvene? Explain.
b. In what direction is the dipole moment in calicene? Explain.


fulvene

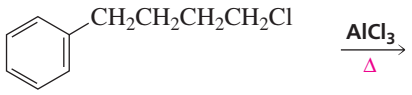

calicene

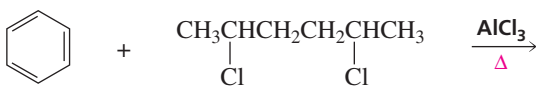
34. Purine is a heterocyclic compound with four nitrogen atoms.
    a. Which nitrogen is most apt to be protonated?
    b. Which nitrogen is least apt to be protonated?



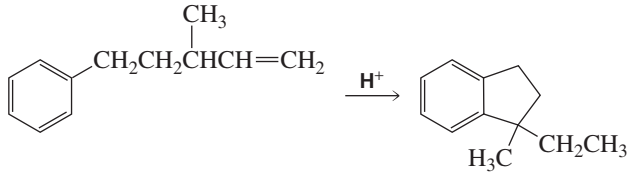
purine

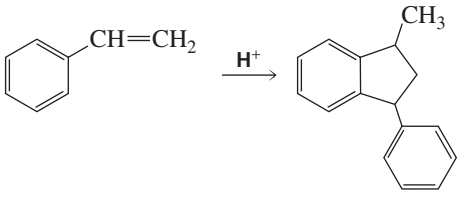
35. Give the product of each of the following reactions:

a. 

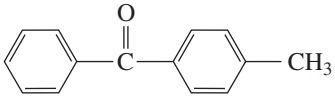
b. 

36. Propose a mechanism for each of the following reactions:

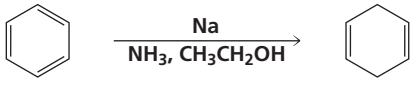
a. 

b. 

37. Show two ways that the following compound could be synthesized:



38. In a reaction called the Birch reduction, benzene can be partially reduced to 1,4-cyclohexadiene by an alkali metal (Na, Li, or K) in liquid ammonia and a low-molecular-weight alcohol. Propose a mechanism for this reaction. (*Hint:* See Section 6.8.)



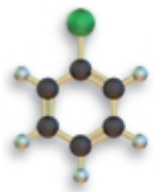
1,4-cyclohexadiene

39. The *principle of least motion,* which states that the reaction that involves the least change in atomic positions or electronic configuration (all else being equal) is favored, has been suggested to explain why the Birch reduction forms only 1,4-hexadiene. How does this account for the observation that no 1,3-cyclohexadiene is obtained from a Birch reduction?

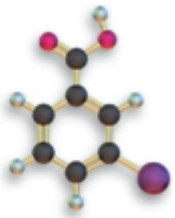
40. Investigation has shown that cyclobutadiene is actually a rectangular molecule rather than a square molecule. In addition, it has been established that there are two different 1,2-dideuterio-1,3-cyclobutadienes. Explain the reason for these unexpected observations.

cyclobutadiene

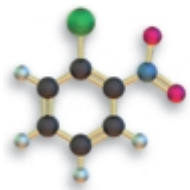
16 Reactions of Substituted Benzenes



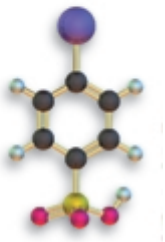
Chlorobenzene



meta-Bromobenzoic acid

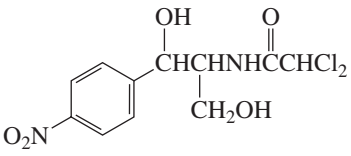


ortho-Chloronitrobenzene

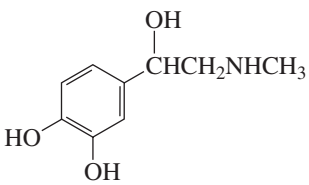


para-Iodobenzenesulfonic acid

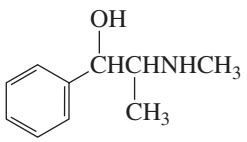
Many substituted benzenes are found in nature. A few that have physiological activity are adrenaline, melanin, ephedrine, chloramphenicol, and mescaline.



chloramphenicol
an antibiotic that is particularly effective against typhoid fever



adrenaline
epinephrine

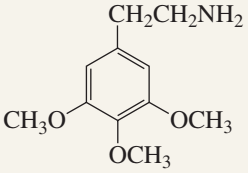


ephedrine
a bronchodilator

Many physiologically active substituted benzenes are not found in nature, but exist because chemists have synthesized them. The now-banned diet drug "fen-phen" is a mixture of two synthetic substituted benzenes: fenfluramine and phentermine. Agent Orange, a defoliant widely used in the 1960s during the Vietnam War, is also a mixture of two synthetic substituted benzenes: 2,4-D and 2,4,5-T. The compound TCDD

PEYOTE CULTS

For several centuries, a peyote cult existed among the Aztecs in Mexico, which later spread to many Native North American tribes. By 1880, a religion that combined Christian beliefs with the Native American use of the peyote cactus had developed in southwestern United States, primarily among Native Americans. The followers of this religion believe that the cactus is divinely endowed to shape each person's life. Currently, the only people in the United States who are legally permitted to use peyote are members of the Native American Church—and then only in their religious rites.

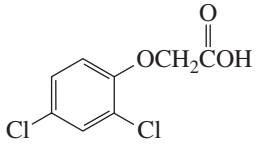


mescaline
active agent of the peyote cactus

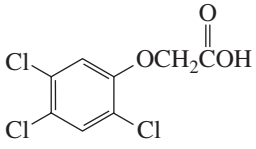
MEASURING TOXICITY

The toxicity of a compound is indicated by its LD_{50} value—the quantity needed to kill 50% of the test animals exposed to the compound. Dioxin, with an LD_{50} value of 0.0006 mg/kg for guinea pigs, is an extremely toxic compound. Compare this with the LD_{50} values of 0.96 mg/kg for strychnine and 15 mg/kg for sodium cyanide—far less toxic compounds. One of the most toxic agents known is the botulism toxin, with an LD_{50} value of about 1×10^{-8} mg/kg.

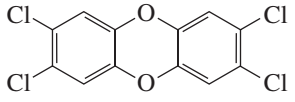
(known as dioxin) is a contaminant formed during the manufacture of Agent Orange. TCDD has been implicated as the causative agent behind various symptoms suffered by those exposed to Agent Orange during the war.



2,4-dichlorophenoxyacetic acid
2,4-D

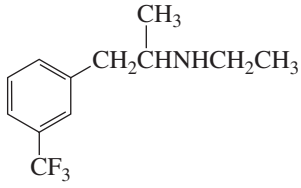


2,4,5-trichlorophenoxyacetic acid
2,4,5-T

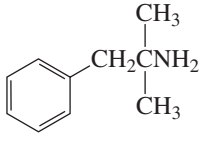


2,3,7,8-tetrachlorodibenzo[*b*,*e*][1,4]dioxin
TCDD

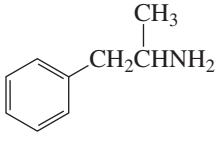
Because of the known physiological activities of adrenaline and mescaline, chemists have synthesized compounds with similar structures. One such compound is amphetamine, a central nervous system stimulant. Amphetamine and a close relative, methamphetamine, are used clinically as appetite suppressants. Methamphetamine is the street drug known as "speed" because of its rapid and intense psychological effects. Two other synthetic substituted benzenes, BHA and BHT, are preservatives (see Section 9.8) found in a wide variety of packaged foods. These compounds represent just a few of the many substituted benzenes that have been synthesized for commercial use by the chemical and pharmaceutical industries.



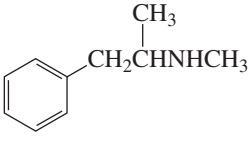
fenfluramine



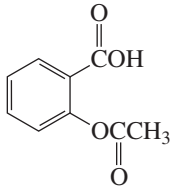
phentermine



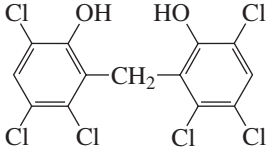
amphetamine



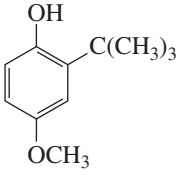
methamphetamine
"speed"



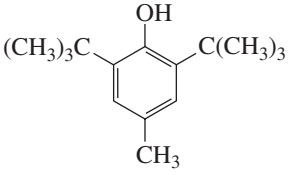
acetylsalicylic acid
aspirin



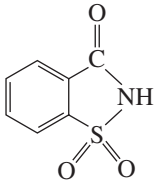
hexachlorophene
a disinfectant



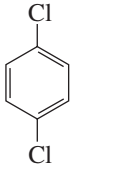
butylated hydroxyanisole
BHA
a food antioxidant



butylated hydroxytoluene
BHT
a food antioxidant



saccharin



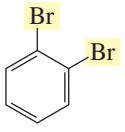
***p*-dichlorobenzene**
mothballs and air fresheners

In Chapter 15, we looked at the reactions benzene undergoes and we saw how monosubstituted benzenes are named. Now we will see how disubstituted and polysubstituted benzenes are named, and then we will look at the reactions of *substituted benzenes*. The physical properties of several substituted benzenes are given in Appendix I.

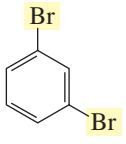
16.1 Nomenclature of Disubstituted and Polysubstituted Benzenes

Disubstituted Benzenes

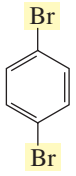
The relative positions of two substituents on a benzene ring can be indicated either by numbers or by the prefixes *ortho, meta*, and *para*. Adjacent substituents are called *ortho*, substituents separated by one carbon are called *meta*, and substituents located opposite one another are designated *para*. Often, only their abbreviations (*o*, *m*, *p*) are used in naming compounds.



1,2-dibromobenzene
***ortho*-dibromobenzene**
***o*-dibromobenzene**

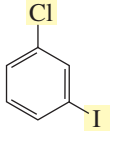


1,3-dibromobenzene
***meta*-dibromobenzene**
***m*-dibromobenzene**

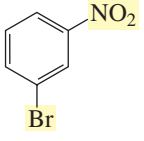


1,4-dibromobenzene
***para*-dibromobenzene**
***p*-dibromobenzene**

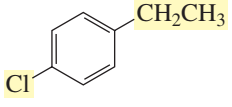
If the two substituents are different, they are listed in alphabetical order. The first stated substituent is given the 1-position, and the ring is numbered in the direction that gives the second substituent the lowest possible number.



1-chloro-3-iodobenzene
***meta*-chloroiodobenzene**
not
1-iodo-3-chlorobenzene or
***meta*-iodochlorobenzene**

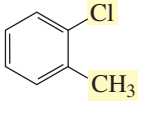


1-bromo-3-nitrobenzene
***meta*-bromonitrobenzene**

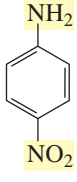


1-chloro-4-ethylbenzene
***para*-chloroethylbenzene**

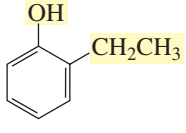
If one of the substituents can be incorporated into a name (Section 15.7), that name is used and the incorporated substituent is given the 1-position.



2-chlorotoluene
***ortho*-chlorotoluene**
not
***ortho*-chloromethylbenzene**

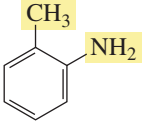


4-nitroaniline
***para*-nitroaniline**
not
***para*-aminonitrobenzene**

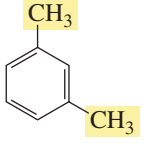


2-ethylphenol
***ortho*-ethylphenol**
not
***ortho*-ethylhydroxybenzene**

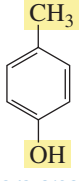
A few disubstituted benzenes have names that incorporate both substituents.



***ortho*-toluidine**



***meta*-xylene**

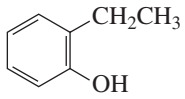


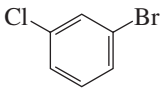
***para*-cresol**
used as a wood preservative until prohibited for environmental reasons

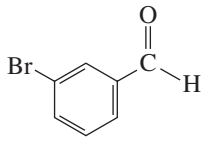
3-D Molecules:
ortho-Toluidine;
meta-Xylene;
para-Cresol

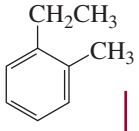
PROBLEM 1◆

Name the following compounds:

a. 

b. 

c. 

d. 

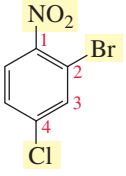
PROBLEM 2◆

Draw structures of the following compounds:

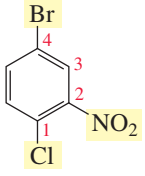
a. *para*-toluidine
b. *meta*-cresol
c. *para*-xylene
d. *ortho*-chlorobenzenesulfonic acid

Polysubstituted Benzenes

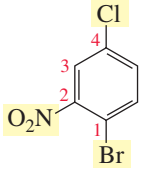
If the benzene ring has more than two substituents, the substituents are numbered so that the lowest possible numbers are used. The substituents are listed in alphabetical order with their appropriate numbers.



2-bromo-4-chloro-1-nitrobenzene

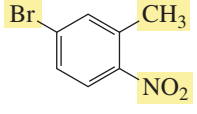


4-bromo-1-chloro-2-nitrobenzene

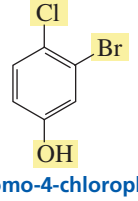


1-bromo-4-chloro-2-nitrobenzene

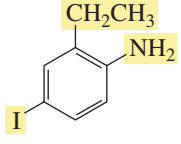
As with disubstituted benzenes, if one of the substituents can be incorporated into a name, that name is used and the incorporated substituent is given the 1-position. The ring is numbered in the direction that results in the lowest possible numbers in the name of the compound.



5-bromo-2-nitrotoluene



3-bromo-4-chlorophenol



2-ethyl-4-iodoaniline

PROBLEM 3◆

Draw the structure of each of the following compounds:

a. *m*-chlorotoluene
b. *p*-bromophenol
c. *o*-nitroaniline
d. *m*-chlorobenzonitrile
e. 2-bromo-4-iodophenol
f. *m*-dichlorobenzene
g. 2,5-dinitrobenzaldehyde
h. *o*-xylene

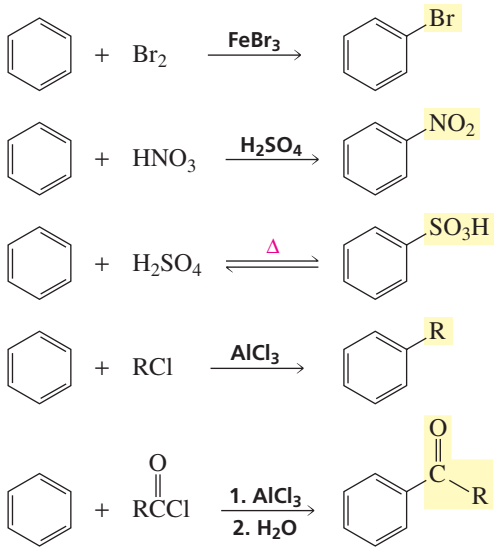
PROBLEM 4◆

Correct the following incorrect names:

a. 2,4,6-tribromobenzene
b. 3-hydroxynitrobenzene
c. *para*-methylbromobenzene
d. 1,6-dichlorobenzene

16.2 Reactions of Substituents on Benzene

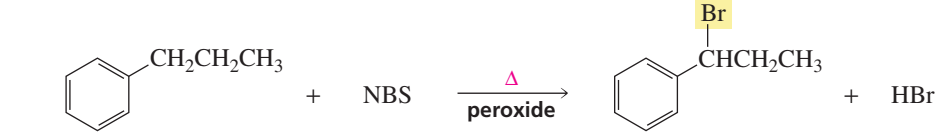
In Chapter 15, you learned how to prepare benzene rings with halo, nitro, sulfonic acid, alkyl, and acyl substituents.



Benzene rings with other substituents can be prepared by first synthesizing one of these substituted benzenes and then chemically changing the substituent. Several of these reactions should be familiar.

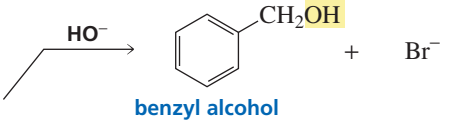
Reactions of Alkyl Substituents

We have seen that a bromine will selectively substitute for a benzylic hydrogen in a radical substitution reaction. (NBS stands for *N*-bromosuccinimide; Section 9.5.)

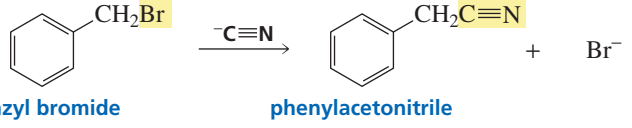


propylbenzene — 1-bromo-1-phenylpropane

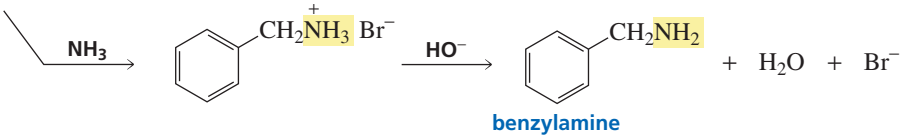
Once a halogen has been placed in the benzylic position, it can be replaced by a nucleophile by means of an S_N2 or an S_N1 reaction (Section 10.8). A wide variety of substituted benzenes can be prepared this way.



benzyl alcohol

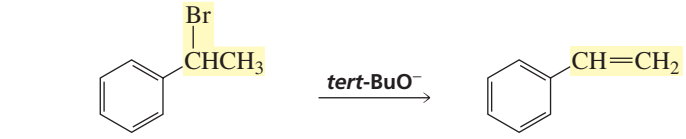


benzyl bromide — phenylacetonitrile



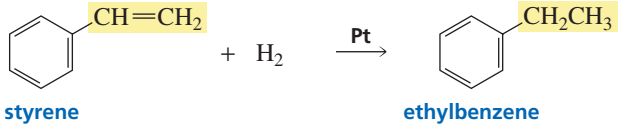
benzylamine

Remember that halo-substituted alkyl groups can also undergo E2 and E1 reactions (Section 11.8). Notice that a bulky base (*tert*-BuO^-) is used to encourage elimination over substitution.



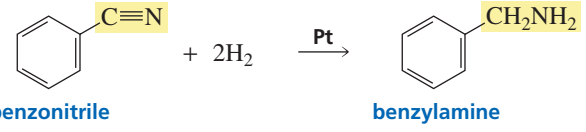
1-bromo-1-phenylethane styrene

Substituents with double and triple bonds can undergo catalytic hydrogenation (Section 4.11). Addition of hydrogen to a double or triple bond is an example of a reduction reaction (Section 4.8). When an organic compound is *reduced*, either the number of C—H bonds in the compound increases or the number of C—O, C—N, or C—X (where X denotes a halogen atom) bonds decreases (Section 20.0).

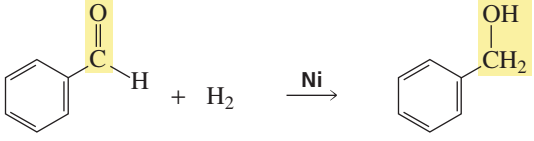


styrene ethylbenzene

3-D Molecules: Benzyl bromide; Styrene; Benzonitrile; Benzaldehyde

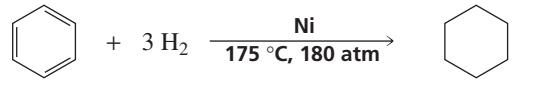


benzonitrile benzylamine



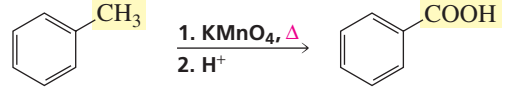
benzaldehyde benzyl alcohol

Recall that benzene is an unusually stable compound (Section 7.11). It, therefore, can be reduced only at high temperature and pressure.



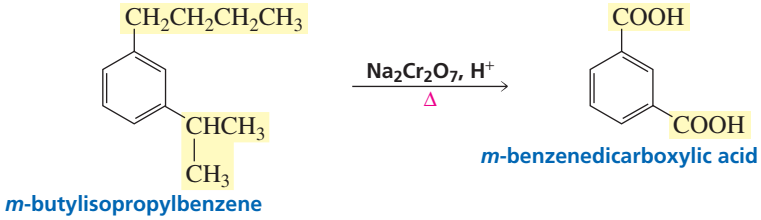
benzene cyclohexane

An alkyl group bonded to a benzene ring can be oxidized to a carboxyl group. When an organic compound is *oxidized*, either the number of C—O, C—N, or C—X (where X denotes a halogen atom) bonds increases or the number of C—H bonds decreases (Section 20.0). Commonly used oxidizing agents are potassium permanganate ($KMnO_4$) or acidic solutions of sodium dichromate (H^+, $Na_2Cr_2O_7$). Because the benzene ring is so stable, it will not be oxidized—only the alkyl group is oxidized.



toluene benzoic acid

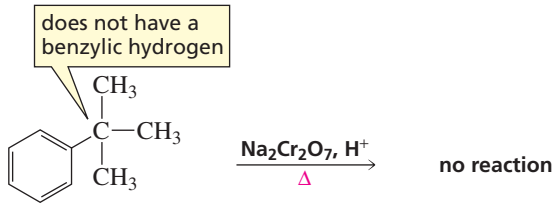
Regardless of the length of the alkyl substituent, it will be oxidized to a COOH group, provided that a hydrogen is bonded to the benzylic carbon.



m-butylisopropylbenzene

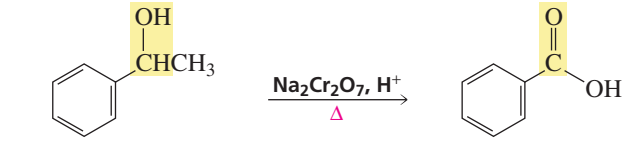
m-benzenedicarboxylic acid

If the alkyl group lacks a benzylic hydrogen, the oxidation reaction will not occur because the first step in the oxidation reaction is removal of a hydrogen from the benzylic carbon.



tert-butylbenzene

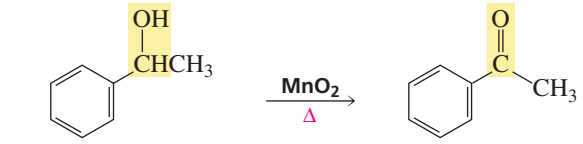
The same reagents that oxidize alkyl substituents will oxidize benzylic alcohols to benzoic acid.



1-phenylethanol

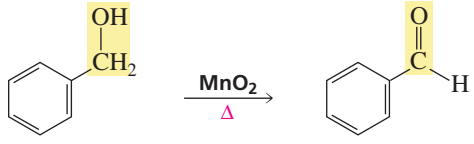
benzoic acid

If, however, a mild oxidizing agent such as MnO_2 is used, benzylic alcohols are oxidized to aldehydes or ketones.



1-phenylethanol

acetophenone

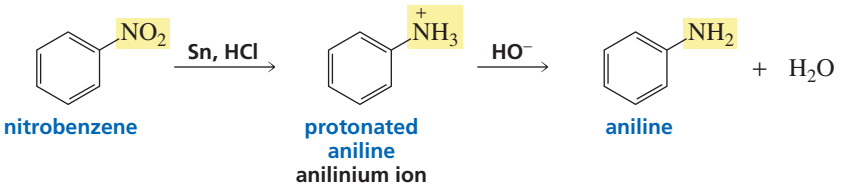


phenylmethanol
benzyl alcohol

benzaldehyde

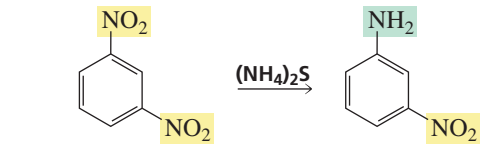
Reducing a Nitro Substituent

A nitro substituent can be reduced to an amino substituent. Either a metal (tin, iron, or zinc) plus an acid (HCl) or catalytic hydrogenation can be used to carry out the reduction. Recall from Section 1.20 that if acidic conditions are employed, the product will be in its acidic form (anilinium ion). When the reaction is over, base can be added to convert the product into its basic form (aniline).



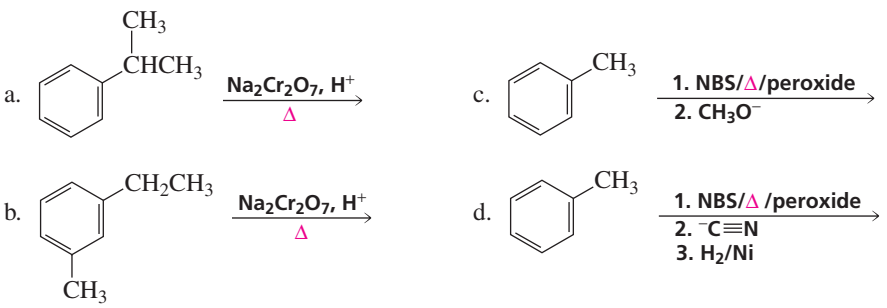
3-D Molecule: Nitrobenzene

It is possible to selectively reduce just one of two nitro groups.



PROBLEM 5◆

Give the product of each of the following reactions:

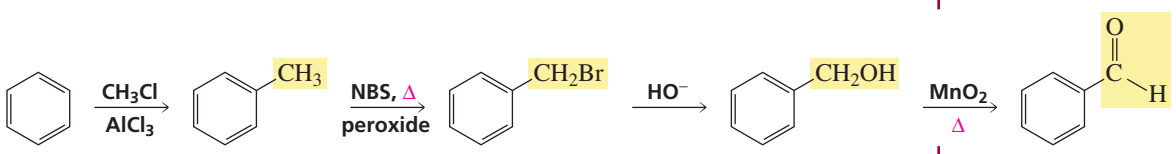


PROBLEM 6 SOLVED

Show how the following compounds could be prepared from benzene:

a. benzaldehyde
b. styrene
c. 1-bromo-2-phenylethane
d. 2-phenyl-1-ethanol
e. aniline
f. benzoic acid

SOLUTION TO 6a



16.3 The Effect of Substituents on Reactivity

Like benzene, substituted benzenes undergo the five electrophilic aromatic substitution reactions discussed in Chapter 15 and listed in Section 16.2: halogenation, nitration, sulfonation, alkylation, and acylation. Now we need to find out whether a substituted benzene is more reactive or less reactive than benzene itself. The answer

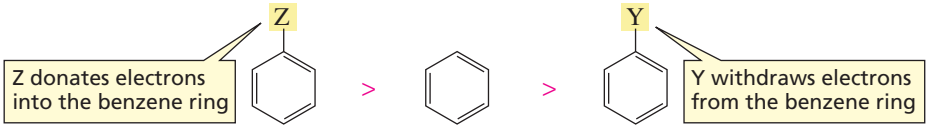
depends on the substituent. Some substituents make the ring more reactive and some make it less reactive than benzene toward electrophilic aromatic substitution.

The slow step of an electrophilic aromatic substitution reaction is the addition of an electrophile to the nucleophilic aromatic ring to form a carbocation intermediate (Section 15.9). *Substituents that are capable of donating electrons into the benzene ring will stabilize both the carbocation intermediate and the transition state leading to its formation* (Section 4.3), *thereby increasing the rate of electrophilic aromatic substitution. In contrast, substituents that withdraw electrons from the benzene ring will destabilize the carbocation intermediate and the transition state leading to its formation, thereby decreasing the rate of electrophilic aromatic substitution* (Section 16.4).Before we see how the carbocation intermediate is stabilized by electron donation and destabilized by electron withdrawal, we will look at the ways in which a substituent can donate or withdraw electrons.

Electron-donating substituents increase the reactivity of the benzene ring toward electrophilic aromatic substitution.

Electron-withdrawing substituents decrease the reactivity of the benzene ring toward electrophilic aromatic substitution.

relative rates of electrophilic substitution



There are two ways substituents can donate electrons into a benzene ring: *inductive* electron donation and electron donation by *resonance*. There are also two ways substituents can withdraw electrons from a benzene ring: *inductive* electron withdrawal and electron withdrawal by *resonance*.

Inductive Electron Donation and Withdrawal

If a substituent that is bonded to a benzene ring is *less electron withdrawing than a hydrogen*, the electrons in the σ bond that attaches the substituent to the benzene ring will move toward the ring more readily than will those in the σ bond that attaches the hydrogen to the ring. Such a substituent donates electrons inductively compared with a hydrogen. Donation of electrons through a σ bond is called **inductive electron donation** (Section 1.18). Alkyl substituents (such as CH_3) donate electrons inductively compared with a hydrogen.

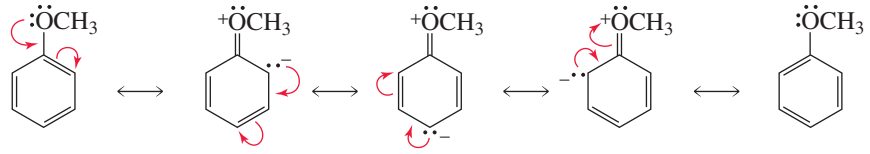
Notice that the electron-donating ability of an alkyl group—not the electron-donating ability of a carbon atom—is compared with that of hydrogen. Carbon is actually slightly less electron donating than hydrogen (because C is more electronegative than H; see Table 1.3), but an alkyl group is more electron donating than hydrogen because of hyperconjugation (Section 4.2).

If a substituent is *more electron withdrawing than a hydrogen*, it will withdraw the σ electrons away from the benzene ring more strongly than will a hydrogen. Withdrawal of electrons through a σ bond is called **inductive electron withdrawal**. The $^{+}NH_3$ group is a substituent that withdraws electrons inductively because it is more electronegative than a hydrogen.

Resonance Electron Donation and Withdrawal

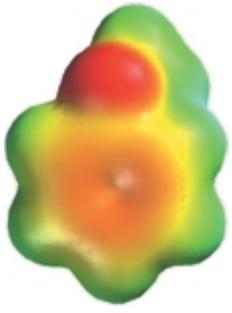
If a substituent has a lone pair on the atom that is directly attached to the benzene ring, the lone pair can be delocalized into the ring; these substituents are said to **donate electrons by resonance**. Substituents such as NH_2, OH, OR, and Cl donate electrons by resonance. These substituents also withdraw electrons inductively because the atom attached to the benzene ring is more electronegative than a hydrogen.

donation of electrons into a benzene ring by resonance



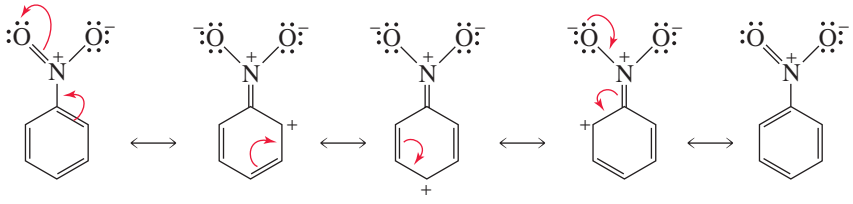
Tutorial:
Donation of electrons into a benzene ring

If a substituent is attached to the benzene ring by an atom that is doubly or triply bonded to a more electronegative atom, the π electrons of the ring can be delocalized onto the substituent; these substituents are said to **withdraw electrons by resonance**. Substituents such as C═O, C≡N, and NO_2 withdraw electrons by resonance. These substituents also withdraw electrons inductively because the atom attached to the benzene ring has a full or partial positive change and, therefore, is more electronegative than a hydrogen.

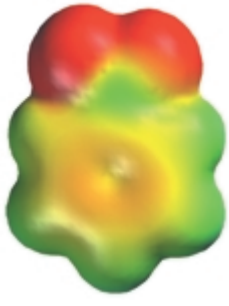


anisole

withdrawal of electrons from a benzene ring by resonance



Tutorial:
Withdrawal of electrons from a benzene ring



nitrobenzene

PROBLEM 7◆

For each of the following substituents, indicate whether it donates electrons inductively, withdraws electrons inductively, donates electrons by resonance, or withdraws electrons by resonance (inductive effects should be compared with a hydrogen; remember that many substituents can be characterized in more than one way):

a. Br

b. CH_2CH_3

c. $\overset{\overset{O}{\|}}{CCH_3}$

d. $NHCH_3$

e. OCH_3

f. $\overset{+}{N}(CH_3)_3$

Relative Reactivity of Substituted Benzenes

The substituents shown in Table 16.1 are listed according to how they affect the reactivity of the benzene ring toward electrophilic aromatic substitution compared with benzene—in which the substituent is a hydrogen. *The* **activating substituents** *make the benzene ring more reactive toward electrophilic substitution; the* **deactivating substituents** *make the benzene ring less reactive toward electrophilic substitution.* Remember that activating substituents donate electrons into the ring and deactivating substituents withdraw electrons from the ring.

All the *strongly activating substituents* donate electrons into the ring by resonance and withdraw electrons from the ring inductively. The fact that they have been found experimentally to be strong activators indicates that electron donation into the ring by resonance is more significant than inductive electron withdrawal from the ring.

strongly activating substituents

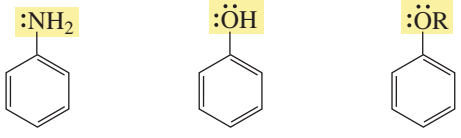
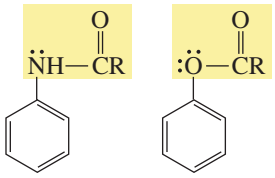


Table 16.1 The Effects of Substituents on the Reactivity of a Benzene Ring Toward Electrophilic Substitution

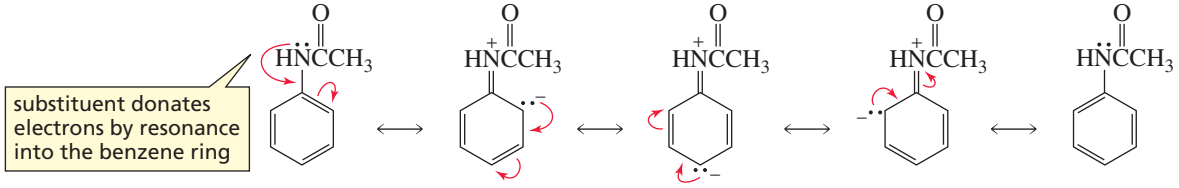
Activating substituents	**Most activating**		
	$-NH_2$	**Strongly activating**	**Ortho/para directing**
	$-NHR$		
	$-NR_2$		
	$-OH$		
	$-OR$		
	$-NHCR$ (O)	**Moderately activating**	
	$-OCR$ (O)		
	$-R$	**Weakly activating**	
	$-Ar$		
	$-CH{=}CHR$		
Standard of comparison →	$-H$		
Deactivating substituents			
	$-F$	**Weakly deactivating**	
	$-Cl$		
	$-Br$		
	$-I$		
	$-CH$ (O)	**Moderately deactivating**	**Meta directing**
	$-CR$ (O)		
	$-COR$ (O)		
	$-COH$ (O)		
	$-CCl$ (O)		
	$-C{\equiv}N$	**Strongly deactivating**	
	$-SO_3H$		
$-\overset{+}{N}H_3$	$-\overset{+}{N}H_2R$		
$-\overset{+}{N}HR_2$	$-\overset{+}{N}R_3$		
	$-NO_2$		
	Most deactivating		

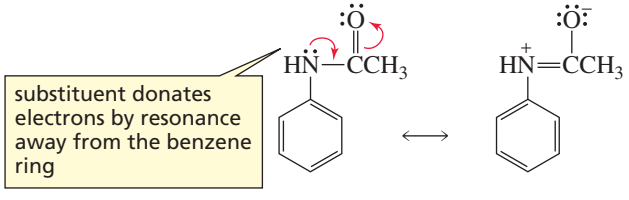
The *moderately activating substituents* also donate electrons into the ring by resonance and withdraw electrons from the ring inductively. Because they are only moderately activating, we know that they donate electrons into the ring by resonance less effectively than do the strongly activating substituents.

moderately activating substituents



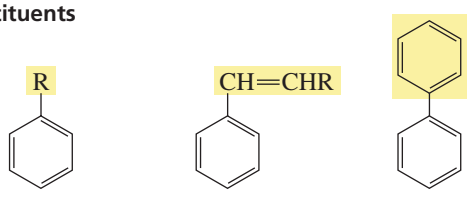
These substituents are less effective at donating electrons into the ring by resonance because, unlike the strongly activating substituents that donate electrons by resonance only *into* the ring, the moderately activating substituents can donate electrons by resonance in two competing directions: *into* the ring and *away from* the ring. The fact that these substituents are activators indicates that, despite their diminished resonance electron donation into the ring, overall they donate electrons by resonance more strongly than they withdraw electrons inductively.





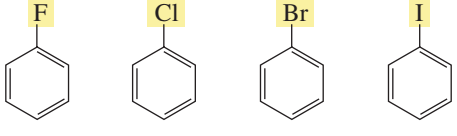
Alkyl, aryl, and CH═CHR groups are *weakly activating substituents*. We have seen that an alkyl substituent, compared with a hydrogen, donates electrons inductively. Aryl and CH═CHR groups can donate electrons into the ring by resonance and can withdraw electrons from the ring by resonance. The fact that they are weak activators indicates that they are slightly more electron donating than they are electron withdrawing.

weakly activating substituents



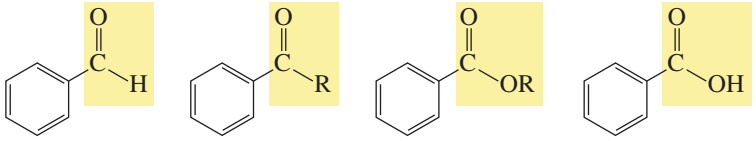
The halogens are *weakly deactivating substituents*; they donate electrons into the ring by resonance and withdraw electrons from the ring inductively. Because the halogens have been found experimentally to be deactivators, we can conclude that they withdraw electrons inductively more strongly than they donate electrons by resonance.

weakly deactivating substituents



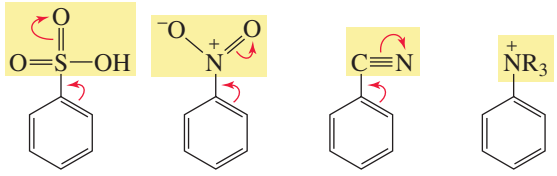
The *moderately deactivating substituents* all have carbonyl groups directly attached to the benzene ring. Carbonyl groups withdraw electrons both inductively and by resonance.

moderately deactivating substituents



The *strongly deactivating substituents* are powerful electron withdrawers. Except for the ammonium ions ($^{+}NH_3$, $^{+}NH_2R$, $^{+}NHR_2$, and $^{+}NR_3$), these substituents withdraw electrons both inductively and by resonance. The ammonium ions have no resonance effect, but the positive charge on the nitrogen atom causes them to strongly withdraw electrons inductively.

strongly deactivating substituents



Take a minute to compare the electrostatic potential maps for anisole, benzene, and nitrobenzene. Notice that an electron-donating substituent (OCH_3) makes the ring more red (more negative), whereas an electron-withdrawing substituent (NO_2) makes the ring less red (less negative).

PROBLEM 8◆

List the members of the following sets of compounds in order of decreasing reactivity toward electrophilic aromatic substitution:

a. benzene, phenol, toluene, nitrobenzene, bromobenzene

b. dichloromethylbenzene, difluoromethylbenzene, toluene, chloromethylbenzene

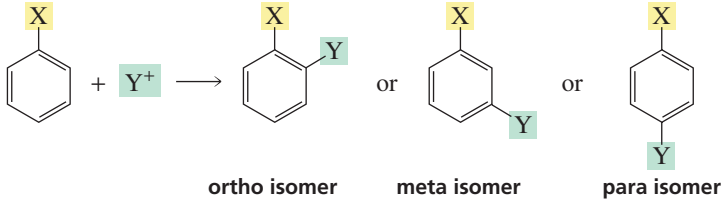
PROBLEM 9 SOLVED

Explain why the halo-substituted benzenes have the relative reactivities shown in Table 16.1.

SOLUTION Table 16.1 shows that fluorine is the least deactivating of the halogen substituents and iodine is the most deactivating. We know that fluorine is the most electronegative of the halogens, which means that it is best at withdrawing electrons inductively. Fluorine is also best at donating electrons by resonance because its 2*p* orbital—compared with the 3*p* orbital of chlorine, the 4*p* orbital of bromine, or the 5*p* orbital of iodine—can better overlap with the 2*p* orbital of carbon. So the fluorine substituent is best both at donating electrons by resonance and at withdrawing electrons inductively. Because the table shows that fluorine is the weakest deactivator of the halogens, we can conclude that electron donation by resonance is the more important factor in determining the relative reactivities of halo-substituted benzenes.

16.4 The Effect of Substituents on Orientation

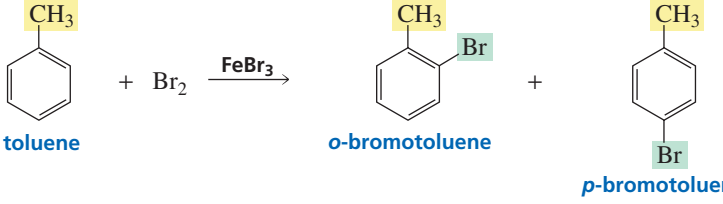
When a substituted benzene undergoes an electrophilic substitution reaction, where does the new substituent attach itself? Is the product of the reaction the ortho isomer, the meta isomer, or the para isomer?



The substituent already attached to the benzene ring determines the location of the new substituent. There are two possibilities: A substituent will direct an incoming substituent either to the ortho *and* para positions, or it will direct an incoming substituent to the meta position. All activating substituents and the weakly deactivating halogens are **ortho–para directors**, and all substituents that are more deactivating than the halogens are **meta directors**. Thus, the substituents can be divided into three groups:

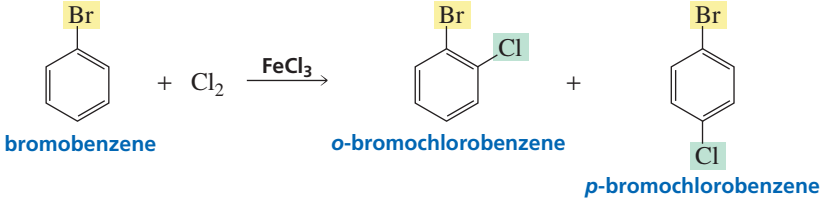
3-D Molecules: Toluene; Bromobenzene

1. All activating substituents direct an incoming electrophile to the ortho and para positions.



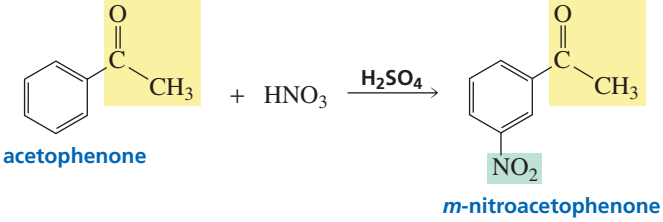
All activating substituents are ortho–para directors.

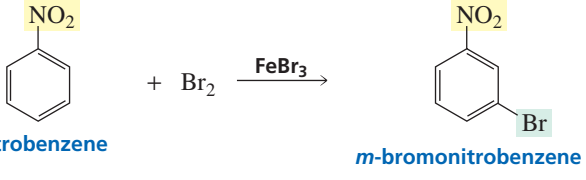
2. The weakly deactivating halogens also direct an incoming electrophile to the ortho and para positions.



The weakly deactivating halogens are ortho–para directors.

3. All moderately deactivating and strongly deactivating substituents direct an incoming electrophile to the meta position.





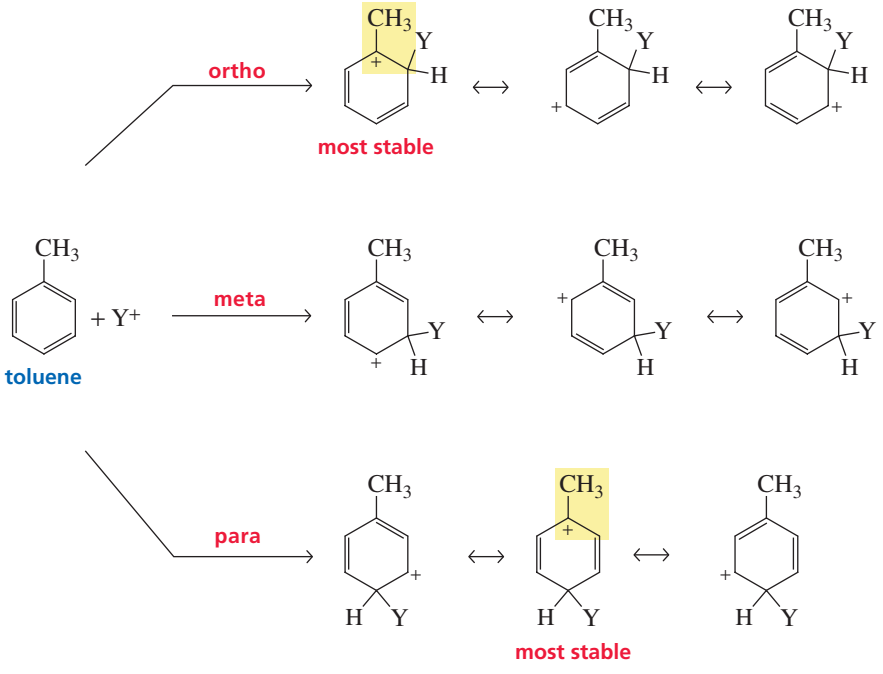
All deactivating substituents (except the halogens) are meta directors.

3-D Molecules: Acetophenone; Nitrobenzene

To understand why a substituent directs an incoming electrophile to a particular position, we must look at the stability of the carbocation intermediate that is formed in the rate-determining step. When a substituted benzene undergoes an electrophilic substitution reaction, three different carbocation intermediates can be formed: an *ortho*-substituted carbocation, a *meta*-substituted carbocation, and a *para*-substituted carbocation (Figure 16.1). The relative stabilities of the three carbocations enable us to determine the preferred pathway of the reaction because the more stable the carbocation, the less energy required to make it and the more likely it is that it will be formed (Section 4.3).

3-D Molecule: Anisole

If a substituent donates electrons *inductively*—a methyl group, for example—the indicated resonance contributors in Figure 16.1 are the most stable; the substituent is attached directly to the positively charged carbon, which the substituent can stabilize by inductive electron donation. These relatively stable resonance contributors are obtained only when the incoming group is directed to an ortho or para position. Therefore, the most stable carbocation is obtained by directing the incoming group to the ortho and para positions. Thus, *any substituent that donates electrons inductively is an ortho–para director*.

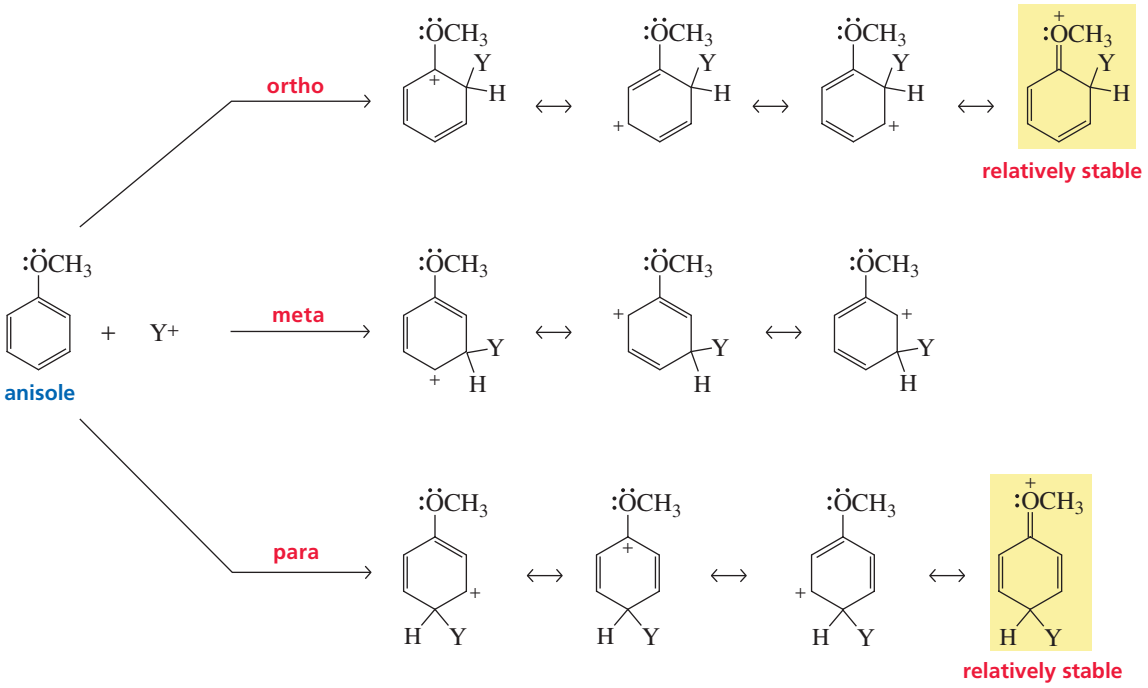


▲ **Figure 16.1**
The structures of the carbocation intermediates formed from the reaction of an electrophile with toluene at the ortho, meta, and para positions.

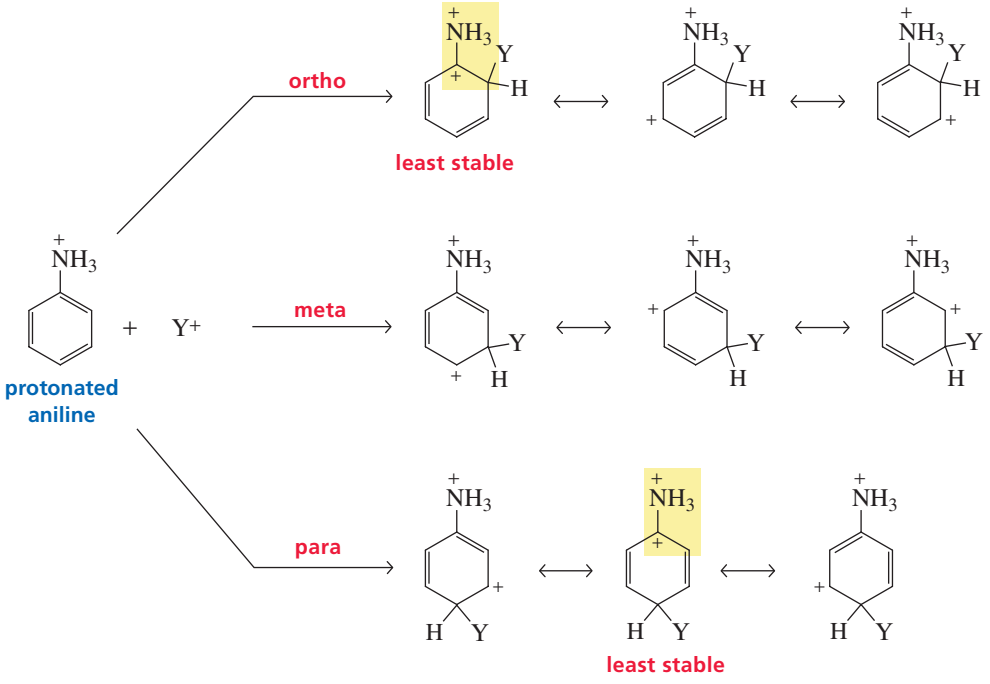
If a substituent donates electrons by *resonance*, the carbocations formed by putting the incoming electrophile on the ortho and para positions have a fourth resonance contributor (Figure 16.2). This is an especially stable resonance contributor because it is the only one whose atoms (except for hydrogen) all have complete octets. Therefore, *all substituents that donate electrons by resonance are ortho–para directors*.

Tutorial: Intermediates in electrophilic aromatic substitution

Substituents with a positive charge or a partial positive charge on the atom attached to the benzene ring, withdraw electrons inductively from the benzene ring, and most withdraw electrons by resonance as well. For all such substituents, the indicated resonance contributors in Figure 16.3 are the least stable because they have a positive charge on each of two adjacent atoms, so the most stable carbocation is formed when the incoming electrophile is directed to the meta position. Thus, *all substituents that withdraw electrons (except for the halogens, which are ortho–para directors because they donate electrons by resonance) are meta directors*.



▲ **Figure 16.2**
The structures of the carbocation intermediates formed from the reaction of an electrophile with anisole at the ortho, meta, and para positions.



▲ **Figure 16.3**
The structures of the carbocation intermediates formed from the reaction of an electrophile with protonated aniline at the ortho, meta, and para positions.

Notice that the three possible carbocation intermediates in Figures 16.1 and 16.3 are the same, except for the substituent. The nature of the substituent determines whether the resonance contributors with the substituent directly attached to the positively charged

carbon are the most stable (electron-donating substituents) or the least stable (electron-withdrawing substituents).

The only deactivating substituents that are ortho–para directors are the halogens, which are the weakest of the deactivators. We have seen that they are deactivators because they inductively withdraw electrons from the ring more strongly than they donate electrons by resonance. The halogens nevertheless are ortho–para directors because of their ability to donate electrons by resonance; they can stabilize the transition states leading to reaction at the ortho and para positions by resonance electron donation (Figure 16.2).

In summary, as shown in Table 16.1, the halogens and all the activating substituents are ortho–para directors. All substituents more deactivating than the halogens are meta directors. Put another way, *all substituents that donate electrons into the ring inductively or by resonance are ortho–para directors, and all substituents that cannot donate electrons into the ring inductively or by resonance are meta directors*.

All substituents that donate electrons into the ring either inductively or by resonance are ortho–para directors.

All substituents that cannot donate electrons into the ring either inductively or by resonance are meta directors.

You don't need to resort to memorization to determine whether a substituent is an ortho–para director or a meta director. It is easy to tell them apart: All ortho–para directors, except for alkyl, aryl, and CH═CHR groups, have at least one lone pair on the atom directly attached to the ring; all meta directors have a positive charge or a partial positive charge on the atom attached to the ring. Take a few minutes to examine the substituents listed in Table 16.1 to convince yourself that this is true.

PROBLEM 10

a. Draw the resonance contributors for nitrobenzene.

b. Draw the resonance contributors for chlorobenzene.

PROBLEM 11◆

What product(s) would result from nitration of each of the following compounds?

a. propylbenzene
b. bromobenzene
c. benzaldehyde
d. benzenesulfonic acid
e. cyclohexylbenzene
f. benzonitrile

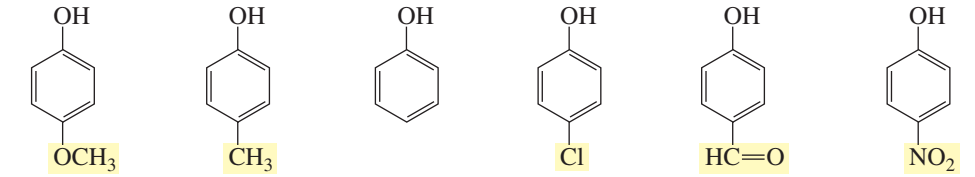
PROBLEM 12◆

Are the following substituents ortho–para directors or meta directors?

a. $CH_2{=}CHC{\equiv}N$
b. NO_2
c. CH_2OH
d. COOH
e. CF_3
f. $N{=}O$

16.5 The Effect of Substituents on pK_a

We have seen that electron-withdrawing substituents increase the acidity of a compound (Sections 1.18 and 7.10). Therefore, when a substituent either withdraws electrons from or donates electrons into a benzene ring, the pK_a values of substituted phenols, benzoic acids, and protonated anilines will reflect this withdrawal or donation. For example, the pK_a of phenol in H_2O at 25 °C is 9.95. The pK_a of *para*-nitrophenol is lower (7.14) because the nitro substituent withdraws electrons from the ring, whereas the pK_a of *para*-methyl phenol is higher (10.19) because the methyl substituent donates electrons into the ring.

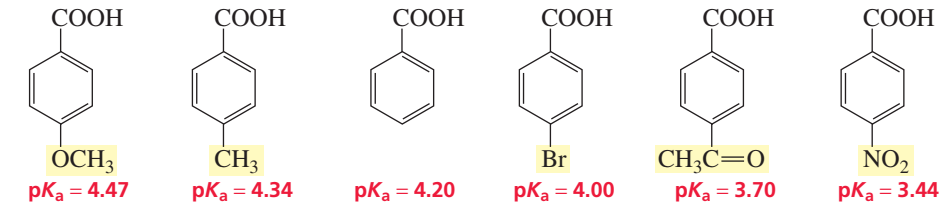


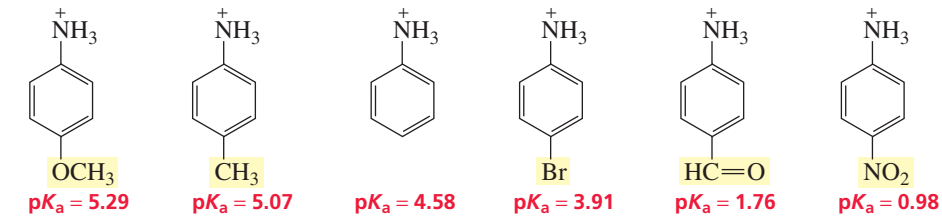
Tutorial:
Effect of substituents on pK_a

Take a minute to compare the influence a substituent has on the reactivity of a benzene ring toward electrophilic substitution with its effect on the pK_a of phenol. Notice that the more strongly deactivating the substituent, the lower the pK_a of the phenol; and the more strongly activating the substituent, the higher the pK_a of the phenol. In other words, *electron withdrawal decreases reactivity toward electrophilic substitution and increases acidity, whereas electron donation increases reactivity toward electrophilic substitution and decreases acidity*.

The more deactivating (electron withdrawing) the substituent, the more it increases the acidity of a COOH, an OH, or an $^+NH_3$ group attached to a benzene ring.

A similar substituent effect on pK_a is observed for substituted benzoic acids and substituted protonated anilines.





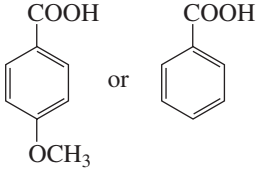
PROBLEM 13◆

Which of the compounds in each of the following pairs is more acidic?

a. CH_3COH or $ClCH_2COH$

b. O_2NCH_2COH or $O_2NCH_2CH_2COH$

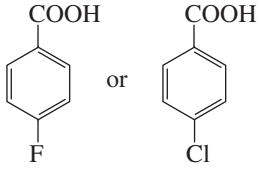
c. CH_3CH_2COH or $H_3\overset{+}{N}CH_2COH$

d. 

e. $HOCCH_2COH$ or $^-OCCH_2COH$

f. $HCOH$ or CH_3COH

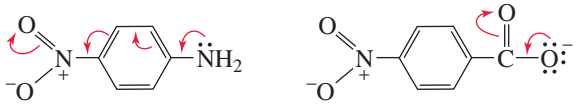
g. FCH_2COH or $ClCH_2COH$

h. 

PROBLEM-SOLVING STRATEGY

The *para*-nitroanilinium ion is 3.60 pK_a units more acidic than the anilinium ion (pK_a = 0.98 versus 4.58), but *para*-nitrobenzoic acid is only 0.76 pK_a unit more acidic than benzoic acid (pK_a = 3.44 versus 4.20). Explain why the nitro substituent causes a large change in pK_a in the one case and a small change in pK_a in the other.

Don't expect to be able to solve this kind of problem simply by reading it. First, you need to remember that the acidity of a compound depends on the stability of its conjugate base (Sections 1.18 and 7.10). Next, draw structures of the conjugate bases in question and compare their stabilities.



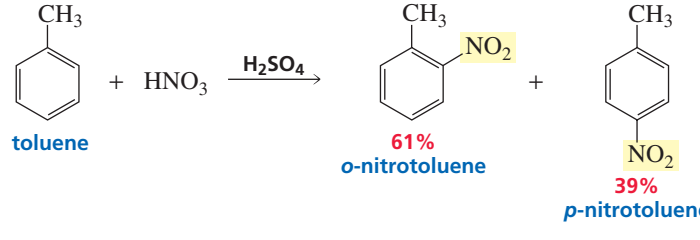
When a proton is lost from the *para*-nitroanilinium ion, the electrons that are left behind are shared by five atoms. (Draw resonance contributors if you want to see which atoms share the electrons.) When a proton is lost from *para*-nitrobenzoic acid, the electrons that are left behind are shared by two atoms. In other words, loss of a proton leads to greater electron delocalization in one base than in the other base. Because electron delocalization stabilizes a compound, we now know why the addition of a nitro substituent has a greater effect on the acidity of an anilinium ion than on benzoic acid. Now continue on to Problem 14.

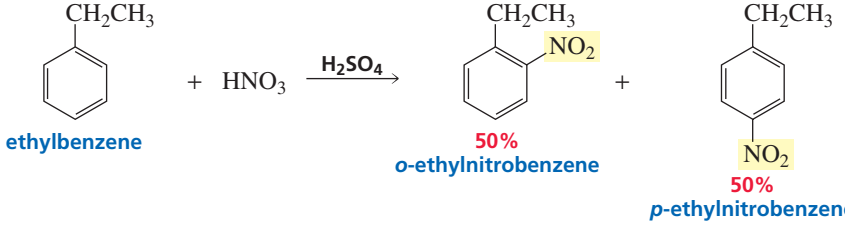
PROBLEM 14

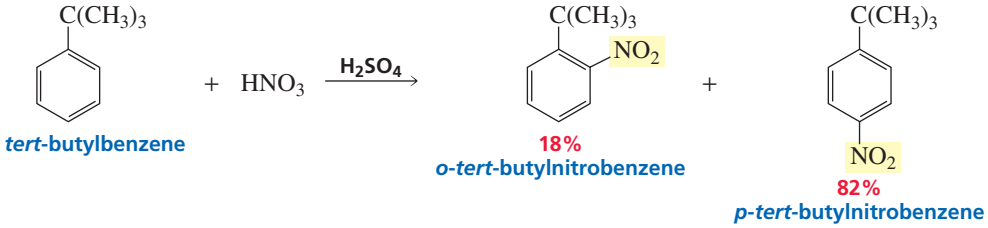
p-Nitrophenol has a pK_a of 7.14, whereas the pK_a of *m*-nitrophenol is 8.39. Explain.

16.6 The Ortho–Para Ratio

When a benzene ring with an ortho–para-directing substituent undergoes an electrophilic aromatic substitution reaction, what percentage of the product is the ortho isomer and what percentage is the para isomer? Solely on the basis of probability, one would expect more of the ortho product because there are two ortho positions available to the incoming electrophile and only one para position. The ortho position, however, is sterically hindered, whereas the para position is not. Consequently, the para isomer will be formed preferentially if either the substituent on the ring or the incoming electrophile is large. The following nitration reactions illustrate the decrease in the ortho–para ratio with an increase in the size of the alkyl substituent:



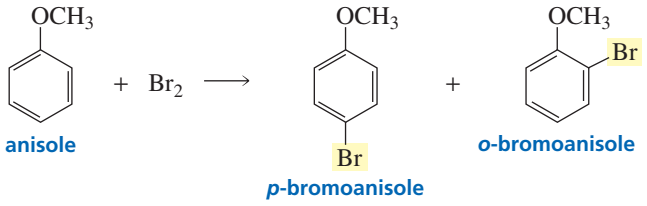




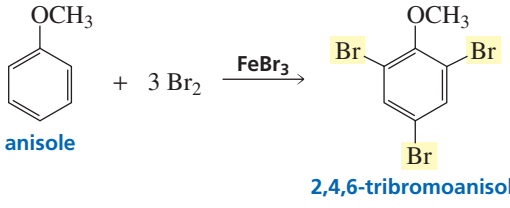
Fortunately, the difference in the physical properties of the ortho- and para-substituted isomers is sufficient to allow them to be easily separated. Consequently, electrophilic aromatic substitution reactions that lead to both ortho and para isomers are useful in synthetic schemes because the desired product can be easily separated from the reaction mixture.

16.7 Additional Considerations Regarding Substituent Effects

It is important to know whether a substituent is activating or deactivating in determining the conditions needed to carry out a reaction. For example, methoxy and hydroxy substituents are so strongly activating that halogenation is carried out without the Lewis acid ($FeBr_3$ or $FeCl_3$) catalyst.

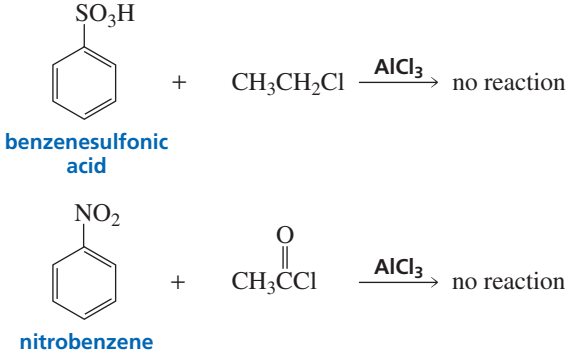


If the Lewis acid catalyst and excess bromine are used, the tribromide is obtained.

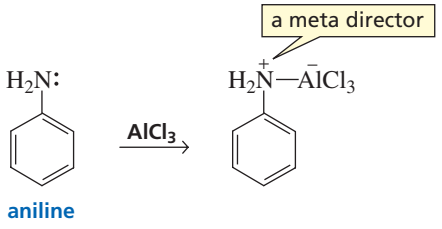


All Friedel–Crafts reactions require the Lewis acid catalyst. However, if there is a meta director on the ring (remember that all meta directors are moderate or strong deactivators), the ring will be too unreactive to undergo either Friedel–Crafts acylation or Friedel–Crafts alkylation.

A benzene ring with a meta director cannot undergo a Friedel–Crafts reaction.



Aniline and *N*-substituted anilines also do not undergo Friedel–Crafts reactions. The lone pair on the amino group will complex with the Lewis acid ($AlCl_3$) that is needed to carry out the reaction, converting the NH_2 substituent into a deactivating meta director. As we have just seen, Friedel–Crafts reactions do not occur with benzene rings containing meta-directing substituents.

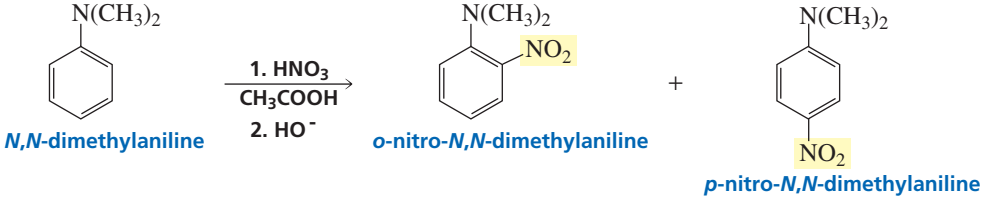


aniline

Phenol and anisole undergo Friedel–Crafts reactions—orienting ortho and para—because oxygen, being a weaker base than nitrogen, does not complex with the Lewis acid.

Aniline also cannot be nitrated because nitric acid is an oxidizing agent and primary amines are easily oxidized. (Nitric acid and aniline can be an explosive combination.) Tertiary aromatic amines, however, can be nitrated. Because the tertiary amino group is a strong activator, nitration is carried out with nitric acid in acetic acid, a milder combination than nitric acid in sulfuric acid. About twice as much para isomer is formed as ortho isomer.

3-D Molecules: *N,N*-Dimethylaniline; *o*-Nitro-*N,N*-dimethylaniline



N,N-dimethylaniline — *o*-nitro-*N,N*-dimethylaniline — *p*-nitro-*N,N*-dimethylaniline

PROBLEM 15◆

Give the products, if any, of each of the following reactions:

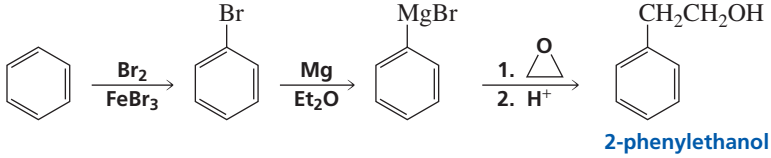
a. benzonitrile + methyl chloride + $AlCl_3$
b. aniline + 3 Br_2
c. benzoic acid + CH_3CH_2Cl + $AlCl_3$
d. benzene + 2 CH_3Cl + $AlCl_3$

PROBLEM 16

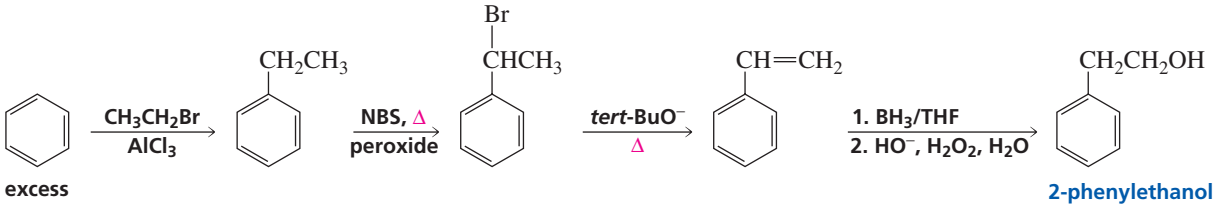
When *N,N*-dimethylaniline is nitrated, some *meta*-nitro-*N,N*-dimethylaniline is formed. Why does the meta isomer form? (*Hint:* The pK_a of *N,N*-dimethylaniline is 5.07, and more meta isomer is formed if the reaction is carried out at pH = 3.5 than if it is carried out at pH = 4.5.)

16.8 Designing a Synthesis III: Synthesis of Monosubstituted and Disubstituted Benzenes

As the number of reactions with wich we are familiar increases, we have more reactions to choose from when we design a synthesis. For example, we can now design two very different routes for the synthesis of 2-phenylethanol from benzene.



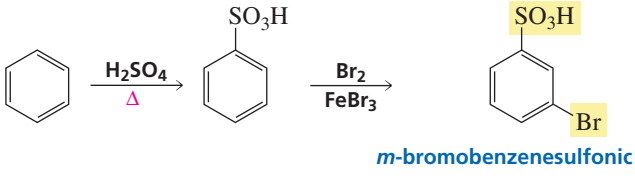
2-phenylethanol



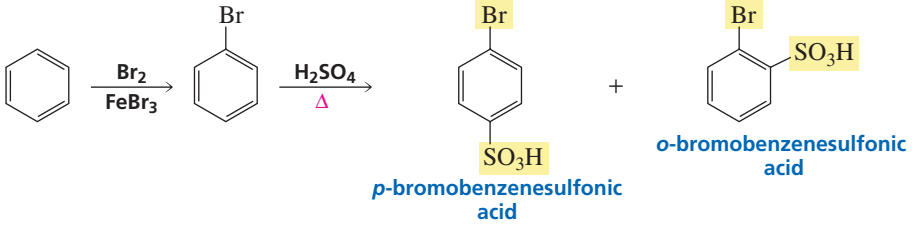
Which route we choose depends on how easy it is to carry out the required reactions and also on the expected yield of the target molecule (the desired product). For example, the first route shown for the synthesis of 2-phenylethanol is the better procedure. The second route has more steps; it requires excess benzene to prevent polyalkylation;it uses a radical reaction that can produce unwanted side products; the yield of the elimination reaction is not high (because some substitution product is formed as well); and hydroboration–oxidation is not an easy reaction to carry out.

In designing the synthesis of disubstituted benzenes, you must consider carefully the order in which the substituents are to be placed on the ring. For example, if you want to synthesize *meta*-bromobenzenesulfonic acid, the sulfonic acid group has to be placed on the ring first because that group will direct the bromo substituent to the desired meta position.

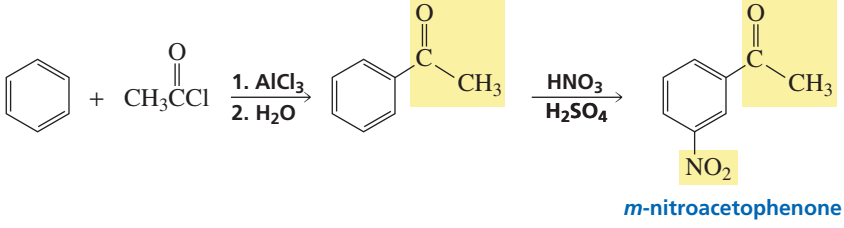
Tutorial:
Multistep synthesis of disubstituted benzenes



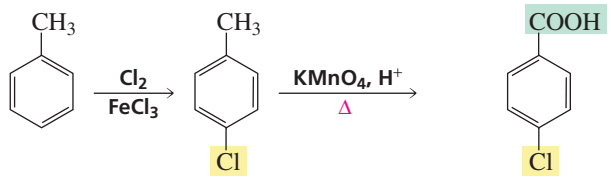
However, if the desired product is *para*-bromobenzenesulfonic acid, the order of the two reactions must be reversed because only the bromo substituent is an ortho–para director.



Both substituents of *meta*-nitroacetophenone are meta directors. However, the Friedel–Crafts acylation reaction must be carried out first because the benzene ring of nitrobenzene is too deactivated to undergo a Friedel–Crafts reaction (Section 16.7).

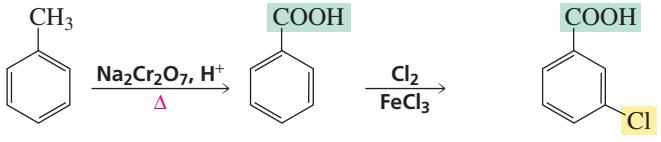


It is also important to determine the point in a reaction sequence at which a substituent should be chemically modified. In the synthesis of *para*-chlorobenzoic acid from toluene, the methyl group is oxidized after it directs the chloro substituent to the para position. (*ortho*-Chlorobenzoic acid is also formed in this reaction.)



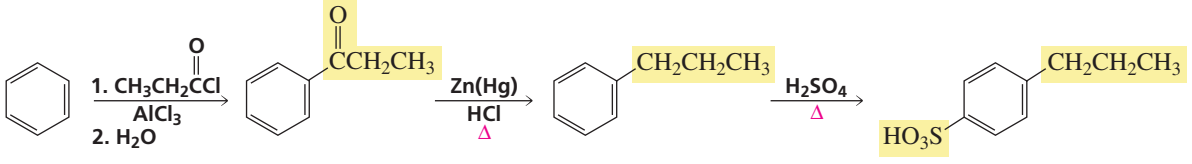
para-chlorobenzoic acid

In the synthesis of *meta*-chlorobenzoic acid, the methyl group is oxidized before chlorination because a meta director is needed to obtain the desired product.



meta-chlorobenzoic acid

In the following synthesis of *para*-propylbenzenesulfonic acid, the type of reaction employed, the order in which the substituents are put on the benzene ring, and the point at which a substituent is chemically modified must all be considered: The straight-chain propyl substituent must be put on the ring by a Friedel–Crafts acylation reaction because of the carbocation rearrangement that would occur with a Friedel–Crafts alkylation reaction. The Friedel–Crafts acylation must be carried out before sulfonation because acylation could not be carried out on a ring with a strongly deactivating sulfonic acid substituent, and the sulfonic acid group is a meta director. Finally, the sulfonic acid group must be put on the ring after the carbonyl group is reduced to a methylene group, so that the sulfonic acid group will be directed primarily to the para position by the alkyl group.



para-propylbenzenesulfonic acid

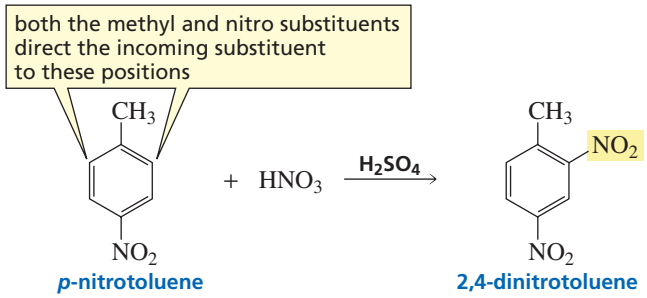
PROBLEM 17

Show how each of the following compounds can be synthesized from benzene:

a. *p*-chloroaniline
b. *m*-chloroaniline
c. *p*-nitrobenzoic acid
d. *m*-nitrobenzoic acid
e. *m*-bromopropylbenzene
f. *o*-bromopropylbenzene
g. 1-phenyl-2-propanol
h. 2-phenylpropene

16.9 Synthesis of Trisubstituted Benzenes

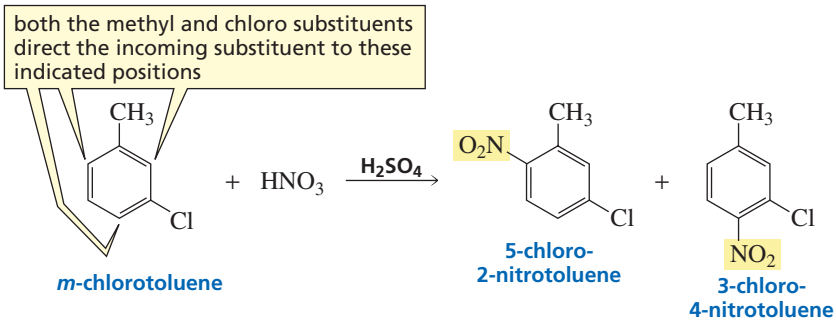
When a disubstituted benzene undergoes an electrophilic aromatic substitution reaction, the directing effect of both substituents has to be considered. If both substituents direct the incoming substituent to the same position, the product of the reaction is easily predicted.



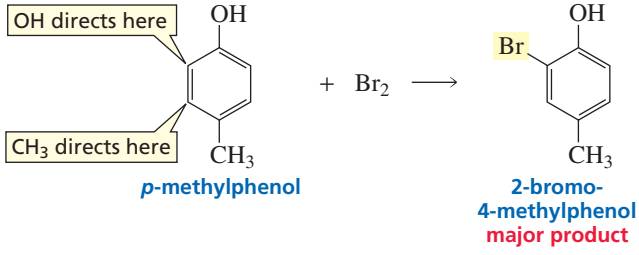
p-nitrotoluene — 2,4-dinitrotoluene

3-D Molecules: *p*-Nitrotoluene; *m*-Chlorotoluene; *p*-Methylphenol; *p*-Chlorotoluene

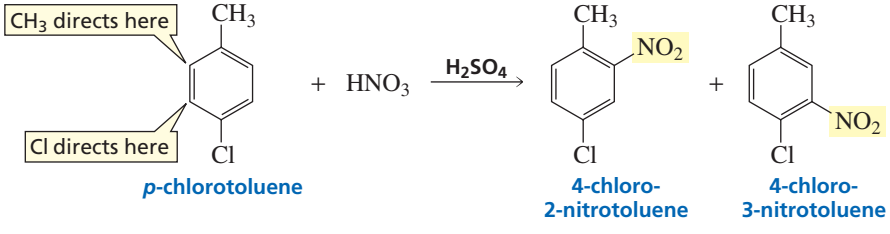
Notice that three positions are activated in the following reaction, but the new substituent ends up on only two of the three positions. Steric hindrance makes the position between the substituents less accessible.



If the two substituents direct the new substituent to different positions, a strongly activating substituent will win out over a weakly activating substituent or a deactivating substituent.



If the two substituents have similar activating properties, neither will dominate and a mixture of products will be obtained.



PROBLEM 18◆

Give the major product(s) of each of the following reactions:

a. nitration of *p*-fluoroanisole

b. chlorination of *o*-benzenedicarboxylic acid

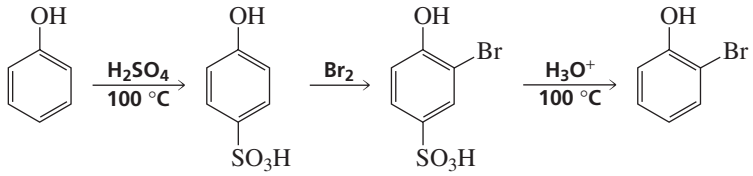
c. bromination of *p*-chlorobenzoic acid

PROBLEM 19 SOLVED

When phenol is treated with Br_2, a mixture of monobromo-, dibromo-, and tribromophenols is obtained. Design a synthesis that would convert phenol primarily to *ortho*-bromophenol.

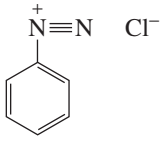
SOLUTION The bulky sulfonic acid group will add preferentially to the para position. Both the OH and SO_3H groups will direct bromine to the position ortho to the OH group.

Heating in dilute acid removes the sulfonic acid group (Section 15.12). Using a sulfonic acid group to block the para position is a method commonly employed to synthesize high yields of ortho-substituted compounds.



16.10 Synthesis of Substituted Benzenes Using Arenediazonium Salts

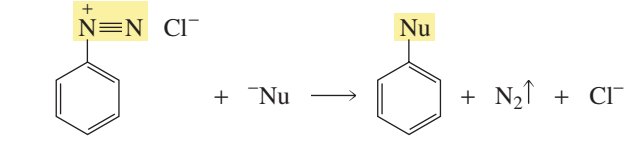
So far, we have learned how to place a limited number of different substituents on a benzene ring—those substituents listed in Section 16.2 and those that can be obtained from these substituents by chemical conversion. However, the kinds of substituents that can be placed on benzene rings can be greatly expanded by the use of **arenediazonium salts**.



an arenediazonium salt

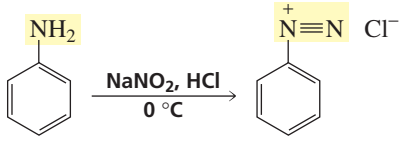
The drive to form a molecule of stable nitrogen gas (N_2) causes the leaving group of a diazonium ion to be easily displaced by a wide variety of nucleophiles. The mechanism by which a nucleophile displaces the diazonium group depends on the nucleophile: Some displacements involve phenyl cations, while others involve radicals.

3-D Molecule: Benzenediazonium chloride



benzenediazonium chloride

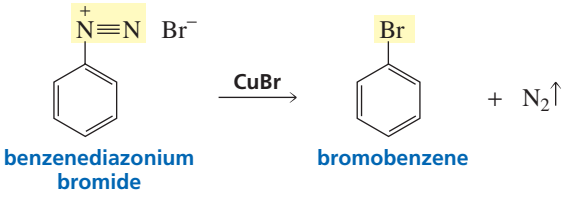
A primary amine can be converted into a diazonium salt by treatment with nitrous acid (HNO_2). Because nitrous acid is unstable, it is formed in situ, using an aqueous solution of sodium nitrite and HCl or HBr; indeed, N_2 is such a good leaving group that the diazonium salt is synthesized at 0 °C and used immediately without isolation. (The mechanism for conversion of a primary amino group [NH_2] to a diazonium group [$^+N{\equiv}N$] is shown in Section 16.12.)



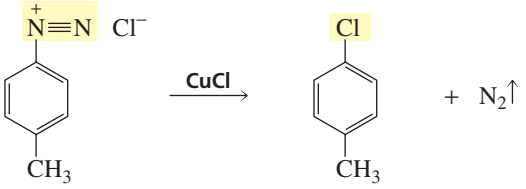
Nucleophiles such as $^-C{\equiv}N$, Cl^-, and Br^- will replace the diazonium group if the appropriate cuprous salt is added to the solution containing the arenediazonium salt. The reaction of an arenediazonium salt with a cuprous salt is known as a **Sandmeyer reaction**.

Sandmeyer reactions

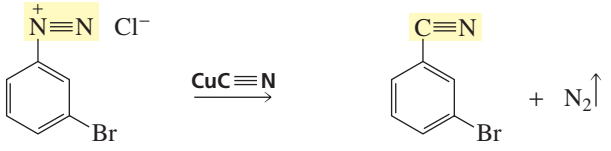
Traugott Sandmeyer (1854–1922) *was born in Switzerland. He received a Ph.D. from the University of Heidelberg and discovered the reaction that bears his name in 1884. He was a scientist at Geigy Co. in Basel, Switzerland.*



benzenediazonium bromide — bromobenzene



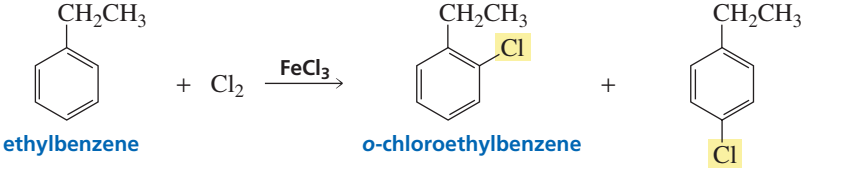
p-toluenediazonium chloride — *p*-chlorotoluene



m-bromobenzenediazonium chloride — *m*-bromobenzonitrile

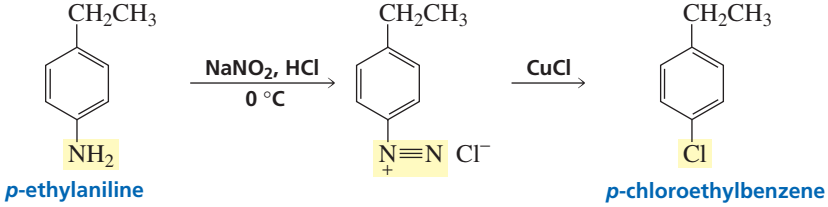
KCl and KBr cannot be used in place of CuCl and CuBr in Sandmeyer reactions; the cuprous salts are required. This indicates that the cuprous ion is involved in the reaction, most likely by serving as a radical initiator (Section 4.10).

Although chloro and bromo substituents can be placed directly on a benzene ring by halogenation, the Sandmeyer reaction can be a useful alternative. For example, if you wanted to make *para*-chloroethylbenzene, chlorination of ethylbenzene would lead to a mixture of the ortho and para isomers.



ethylbenzene — *o*-chloroethylbenzene — *p*-chloroethylbenzene

However, if you started with *para*-ethylaniline and used a Sandmeyer reaction for chlorination, only the desired para product would be formed.



p-ethylaniline — *p*-chloroethylbenzene

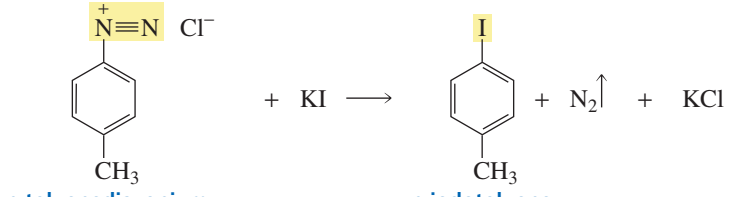
PROBLEM 20

Explain why a diazonium group on a benzene ring cannot be used to direct an incoming substituent to the meta position.

PROBLEM 21

Explain why HBr should be used to generate the benzenediazonium salt if bromobenzene is the desired product of the Sandmeyer reaction and HCl should be used if chlorobenzene is the desired product.

An iodo substituent will replace the diazonium group if potassium iodide is added to the solution containing the diazonium ion.



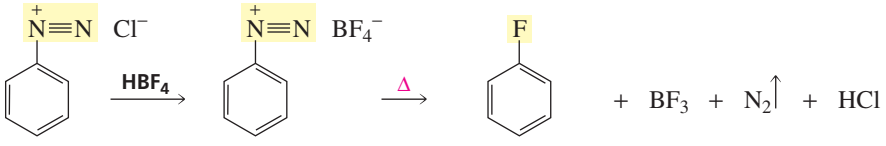
p-toluenediazonium chloride

p-iodotoluene

Fluoro substitution occurs if the arenediazonium salt is heated with fluoroboric acid (HBF_4). This reaction is known as the **Schiemann reaction**.

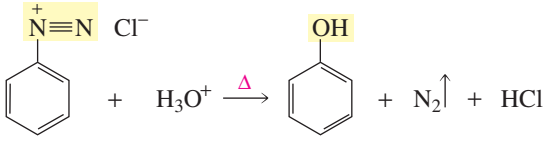
Günther Schiemann (1899–1969) *was born in Germany. He was a professor of chemistry at the Technologische Hochschule in Hanover, Germany.*

Schiemann reaction



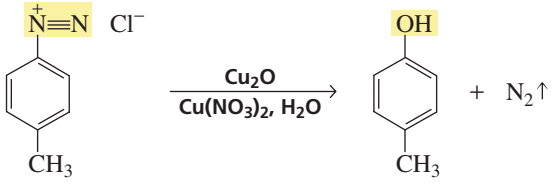
fluorobenzene

If the aqueous solution in which the diazonium salt has been synthesized is acidified and heated, an OH group will replace the diazonium group. (H_2O is the nucleophile.) This is a convenient way to synthesize a phenol.



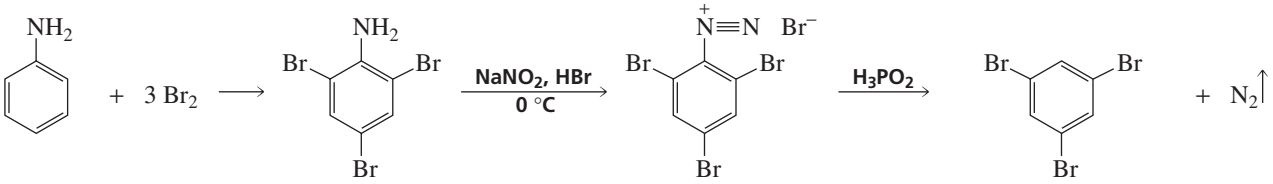
phenol

Phenols can also be prepared at room temperature using cuprous oxide and aqueous cupric nitrate.



p-cresol

A hydrogen will replace a diazonium group if the diazonium salt is treated with hypophosphorous acid (H_3PO_2). This is a useful reaction if an amino group or a nitro group is needed for directing purposes and subsequently must be removed. It would be difficult to envision how 1,3,5-tribromobenzene could be synthesized without such a reaction.



PROBLEM 22

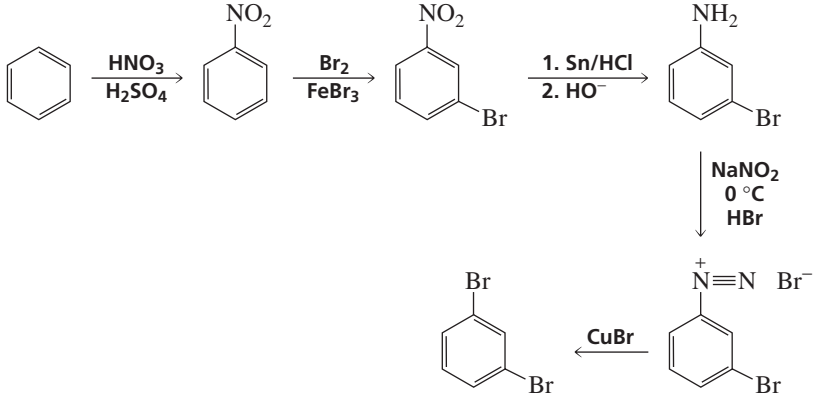
Write the sequence of steps involved in the conversion of benzene into benzenediazonium chloride.

PROBLEM 23 SOLVED

Show how the following compounds could be synthesized from benzene:

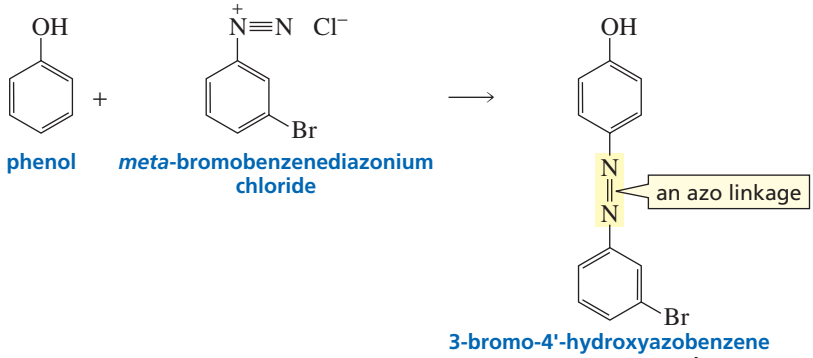
a. *m*-dibromobenzene
b. *m*-bromophenol
c. *o*-chlorophenol
d. *m*-nitrotoluene
e. *p*-methylbenzonitrile
f. *m*-chlorobenzaldehyde

SOLUTION TO 23a A bromo substituent is an ortho–para director, so halogenation cannot be used to introduce both bromo substituents of *m*-dibromobenzene. Knowing that a bromo substituent can be placed on a benzene ring with a Sandmeyer reaction and that the bromo substituent in a Sandmeyer reaction replaces what originally was a meta-directing nitro substituent, we have a route to the synthesis of the target compound.



16.11 The Arenediazonium Ion as an Electrophile

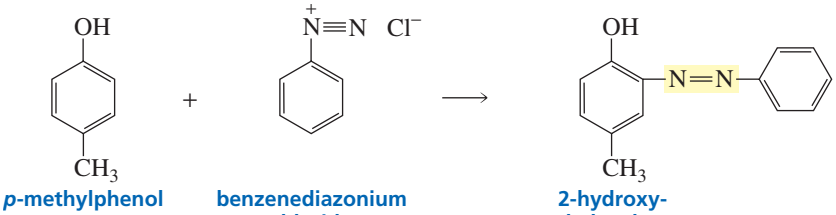
In addition to being used to synthesize substituted benzenes, arenediazonium ions can be used as electrophiles in electrophilic aromatic substitution reactions. Because an arenediazonium ion is unstable at room temperature, it can be used as an electrophile only in electrophilic aromatic substitution reactions that can be carried out well below room temperature. In other words, only highly activated benzene rings (phenols, anilines, and *N*-alkylanilines) can undergo electrophilic aromatic substitution reactions with arenediazonium ion electrophiles. The product of the reaction is an *azo compound*. The N═N linkage is called an **azo linkage**. Because the electrophile is so large, substitution takes place preferentially at the less sterically hindered para position.



phenol — *meta*-bromobenzenediazonium chloride

3-bromo-4'-hydroxyazobenzene
an azo compound

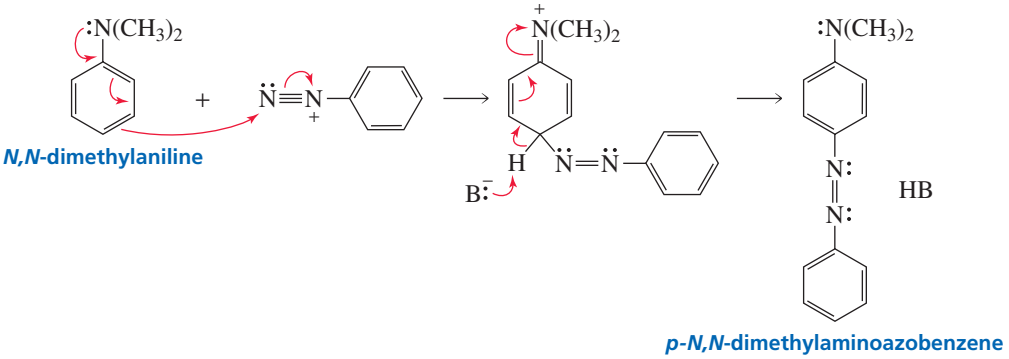
However, if the para position is blocked, substitution will occur at an ortho position.



p-methylphenol — benzenediazonium chloride — 2-hydroxy-5-methylazobenzene

The mechanism for electrophilic aromatic substitution with an arenediazonium ion electrophile is the same as the mechanism for electrophilic aromatic substitution with any other electrophile.

mechanism for electrophilic aromatic substitution using an arenediazonium ion electrophile

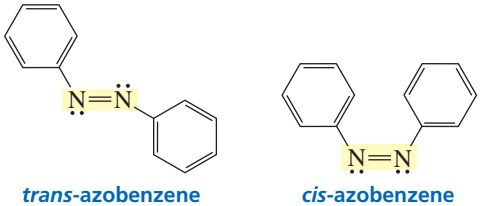


***N,N*-dimethylaniline**

p-*N,N*-dimethylaminoazobenzene

3-D Molecule: *para*-*N*,*N*-Dimethylaminoazobenzene

Azo compounds, like alkenes, can exist in cis and trans forms. Because of steric strain, the trans isomer is considerably more stable than the cis isomer (Section 4.11).



***trans*-azobenzene** ***cis*-azobenzene**

We have seen that azobenzenes are colored compounds because of their extended conjugation and are used commercially as dyes (Section 8.12).

PROBLEM 24

In the mechanism for electrophilic aromatic substitution with a diazonium ion as the electrophile, why does nucleophilic attack occur on the terminal nitrogen atom of the diazonium ion rather than on the nitrogen atom bonded to the benzene ring?

PROBLEM 25

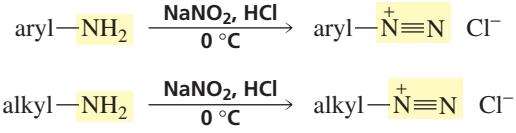
Give the structure of the activated benzene ring and the diazonium ion used in the synthesis of the following compounds:

a. butter yellow b. methyl orange

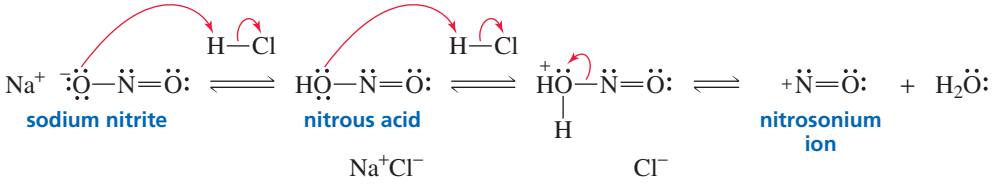
(The structures of these compounds can be found in Section 8.12.)

16.12 Mechanism for the Reaction of Amines with Nitrous Acid

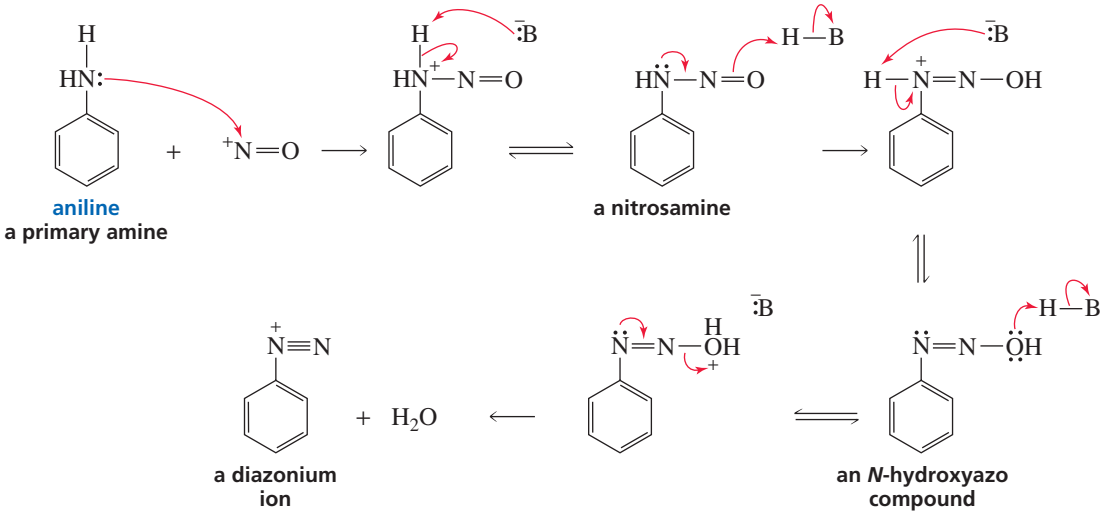
We have seen that the reaction of a primary amine with nitrous acid produces a diazonium salt. Both aryl amines and alkyl amines undergo this reaction, and both follow the same mechanism.



Conversion of a *primary* amino group to a diazonium group requires a nitrosonium ion that is formed when water is eliminated from protonated nitrous acid.



The nitrosonium ion accepts a share of the amino nitrogen's lone pair. Loss of a proton from nitrogen forms a **nitrosamine** (also called an ***N*-nitroso compound** because a nitroso substituent is bonded to a nitrogen). Delocalization of nitrogen's lone pair and protonation of oxygen form a protonated *N*-hydroxyazo compound. This compound is in equilibrium with its nonprotonated form, which can be reprotonated on nitrogen (reverse reaction) or protonated on oxygen (forward reaction). Elimination of water forms the diazonium ion.



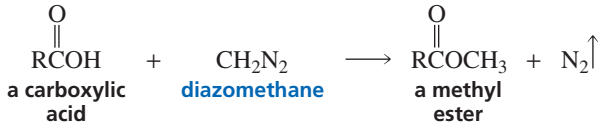
Remember that reactions in which arenediazonium ions are involved must be carried out at 0 °C because they are unstable at higher temperatures. Alkanediazonium ions are even less stable. They lose molecular N_2—even at 0 °C—as they are formed, reacting with whatever nucleophiles are present in the reaction mixture by both S_N1/E1 and S_N2/E2 mechanisms. Because of the mixture of products obtained, alkanediazonium ions are of limited synthetic use.

PROBLEM 26◆

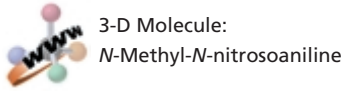
What products would be formed from the reaction of isopropylamine with sodium nitrite and aqueous HCl?

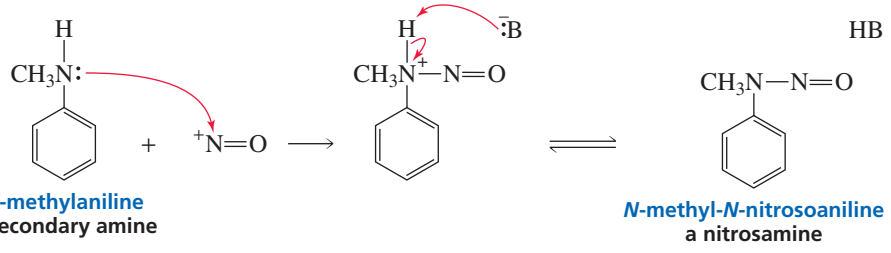
PROBLEM 27

Diazomethane can be used to convert a carboxylic acid into a methyl ester. Propose a mechanism for this reaction.



Secondary aryl and alkyl amines react with a nitrosonium ion to form nitrosamines rather than diazonium ions. The mechanism of the reaction is similar to that for the reaction of a primary amine with a nitrosonium ion, except that the reaction stops at the nitrosamine stage. The reaction stops because a secondary amine, unlike a primary amine, does not have the second proton that must be lost in order to generate the diazonium ion.

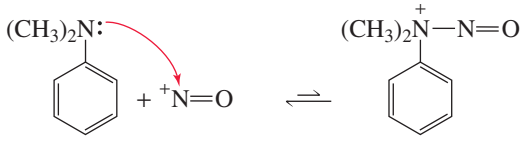

3-D Molecule: *N*-Methyl-*N*-nitrosoaniline



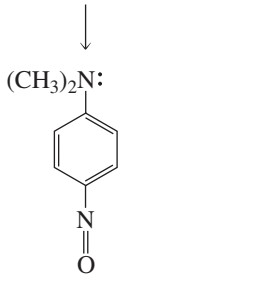
***N*-methylaniline**
a secondary amine

***N*-methyl-*N*-nitrosoaniline**
a nitrosamine

The product formed when the nitrogen of a *tertiary* amine shares its lone pair with a nitrosonium ion cannot be stabilized by loss of a proton. A tertiary aryl amine, therefore, can undergo an electrophilic aromatic substitution reaction with a nitrosonium ion. The product of the reaction is primarily the para isomer because the bulky dialkylamino group blocks approach of the nitrosonium ion to the ortho position.



***N*,*N*-dimethylaniline**
a tertiary amine



***para*-nitroso-*N*,*N*-dimethylaniline**
85%

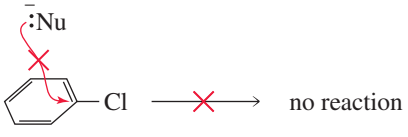
3-D Molecule: *para*-Nitroso-*N*,*N*-dimethylaniline

NITROSAMINES AND CANCER

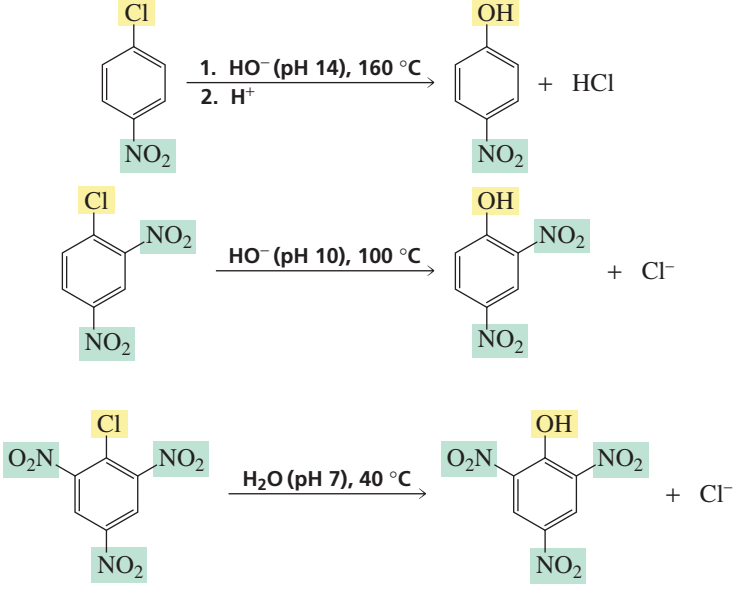
A 1962 outbreak of food poisoning in sheep in Norway was traced to their ingestion of nitrite-treated fish meal. This incident immediately raised concerns about human consumption of nitrite-treated foods, because sodium nitrite is a commonly used food preservative. It can react with naturally occurring secondary amines present in food, to produce nitrosamines, which are known to be carcinogenic. Smoked fish, cured meats, and beer all contain nitrosamines. Nitrosamines are also found in cheese, which is not surprising because some cheeses are preserved with nitrite and cheese is rich in secondary amines. In the United States, consumer groups asked the Food and Drug Administration to ban the use of sodium nitrite as a preservative. This request was vigorously opposed by the meat-packing industry. Despite extensive investigations, it has not been determined whether the small amounts of nitrosamines present in our food pose a hazard to our health. Until this question can be answered, it will be hard to avoid sodium nitrite in our diet. It is worrisome to note, however, that Japan has both one of the highest gastric cancer rates and the highest average ingestion of sodium nitrite. Some good news is that the concentration of nitrosamines present in bacon has been considerably reduced in recent years by adding ascorbic acid—a nitrosamine inhibitor—to the curing mixture. Also, improvements in the malting process have reduced the level of nitrosamines in beer. Dietary sodium nitrite does have a redeeming feature—there is some evidence that it protects against botulism (a type of severe food poisoning).

16.13 Nucleophilic Aromatic Substitution Reactions

We have seen that aryl halides do not react with nucleophiles under standard reaction conditions because the π electron clouds repel the approach of a nucleophile (Section 10.8).



If, however, the aryl halide has one or more substituents that strongly withdraw electrons from the ring by resonance, **nucleophilic aromatic substitution** reactions can occur without using extreme conditions. The electron-withdrawing groups must be positioned ortho or para to the halogen. The greater the number of electron-withdrawing substituents, the easier it is to carry out the nucleophilic aromatic substitution reaction. Notice the different conditions under which the following reactions occur:



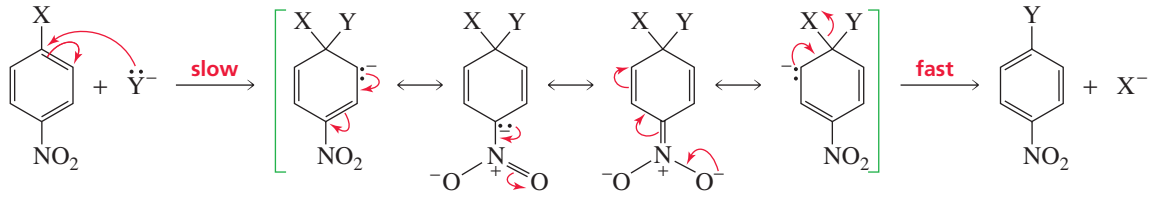
3-D Molecule: 1-Chloro-2,4,6-trinitrobenzene

Electron-withdrawing substituents increase the reactivity of the benzene ring toward nucleophilic substitution and decrease the reactivity of the benzene ring toward electrophilic substitution.

Notice also that the strongly electron-withdrawing substituents that *activate* the benzene ring toward *nucleophilic aromatic substitution* reactions are the same substituents that *deactivate* the ring toward *electrophilic aromatic substitution*. In other words, making the ring less electron rich makes it easier for a nucleophile—but more difficult for an electrophile—to approach the ring. Thus, any substituent that deactivates the benzene ring toward electrophilic substitution activates it toward nucleophilic substitution and vice versa.

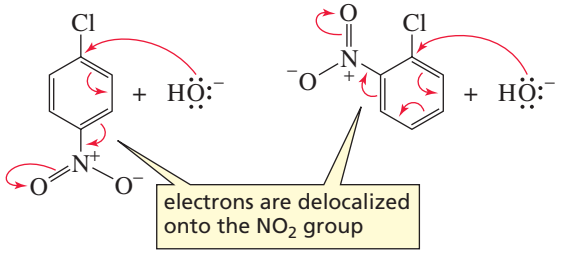
Nucleophilic aromatic substitution takes place by a two-step reaction known as an **S_NAr reaction** (substitution nucleophilic aromatic). In the first step, the nucleophile attacks the carbon bearing the leaving group from a trajectory that is nearly perpendicular to the aromatic ring. (Recall from Section 10.8 that leaving groups cannot be displaced from sp^2 carbon atoms by back-side attack.) Nucleophilic attack forms a resonance-stabilized carbanion intermediate called a *Meisenheimer complex*, after Jakob Meisenheimer (1876–1934). In the second step of the reaction, the leaving group departs, reestablishing the aromaticity of the ring.

general mechanism for nucleophilic aromatic substitution



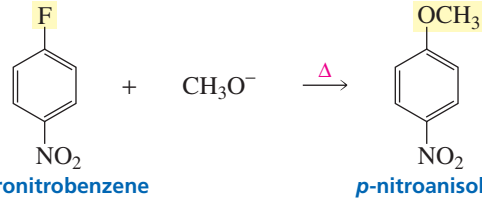
In a nucleophilic aromatic substitution reaction, the incoming nucleophile must be a stronger base than the substituent that is being replaced, because the weaker of the two bases will be the one eliminated from the intermediate.

The electron-withdrawing substituent must be ortho or para to the site of nucleophilic attack because the electrons of the attacking nucleophile can be delocalized onto the substituent only if the substituent is in one of those positions.

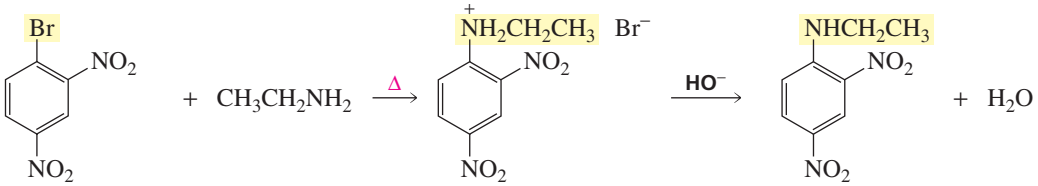


A variety of substituents can be placed on a benzene ring by means of nucleophilic aromatic substitution reactions. The only requirement is that the incoming group be a stronger base than the group that is being replaced.

3-D Molecule:
para-Fluoronitrobenzene



***p*-fluoronitrobenzene** ***p*-nitroanisole**



1-bromo-2,4-dinitrobenzene ***N*-ethyl-2,4-dinitroaniline**

PROBLEM 28

Draw resonance contributors for the carbanion that would be formed if *meta*-chloronitrobenzene could react with hydroxide ion. Why doesn't it react?

PROBLEM 29◆

a. List the following compounds in order of decreasing reactivity toward nucleophilic aromatic substitution:

chlorobenzene 1-chloro-2,4-dinitrobenzene *p*-chloronitrobenzene

b. List the same compounds in order of decreasing reactivity toward electrophilic aromatic substitution.

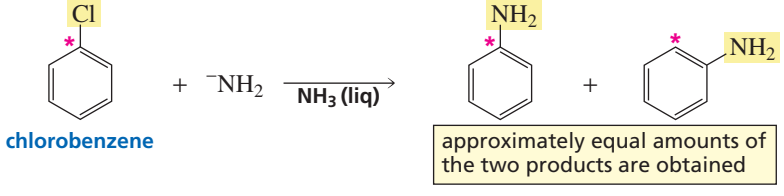
PROBLEM 30

Show how each of the following compounds could be synthesized from benzene:

a. *o*-nitrophenol b. *p*-nitroaniline c. *p*-bromoanisole

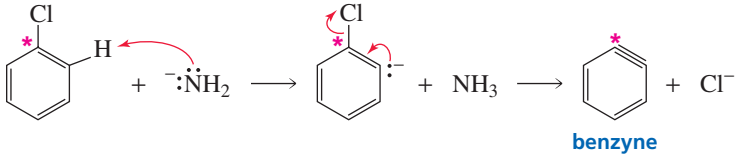
16.14 Benzyne

An aryl halide such as chlorobenzene can undergo a nucleophilic substitution reaction in the presence of a very strong base such as $^{-}NH_2$. There are two surprising features about this reaction: The aryl halide does not have to contain an electron-withdrawing group, and the incoming substituent does not always end up on the carbon vacated by the leaving group. For example, when chlorobenzene—with the carbon to which the chlorine is attached isotopically labeled with ^{14}C—is treated with amide ion in liquid ammonia, aniline is obtained as the product. Half of the product has the amino group attached to the isotopically labeled carbon (denoted by the asterisk) as expected, but the other half has the amino group attached to the carbon adjacent to the labeled carbon.



These are the only products formed. Anilines with the amino group two or three carbons removed from the labeled carbon are not formed.

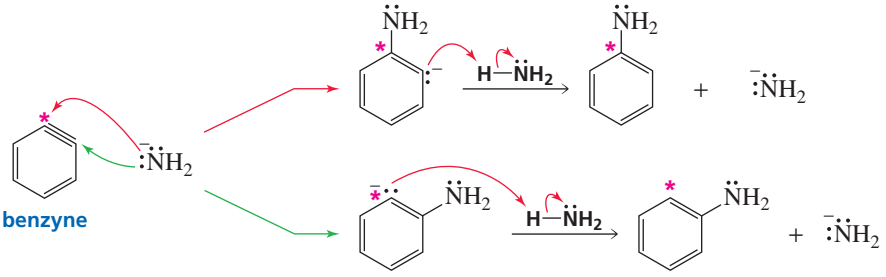
The fact that the two products are formed in approximately equal amounts indicates that the reaction takes place by a mechanism that forms an intermediate in which the two carbons to which the amino group is attached in the product are equivalent. The mechanism that accounts for the experimental observations involves the formation of a **benzyne intermediate**. Benzyne has a triple bond between two adjacent carbon atoms of benzene. In the first step of the mechanism, the strong base ($^{-}NH_2$) removes a proton from the position ortho to the halogen. The resulting anion expels the halide ion, thereby forming benzyne.



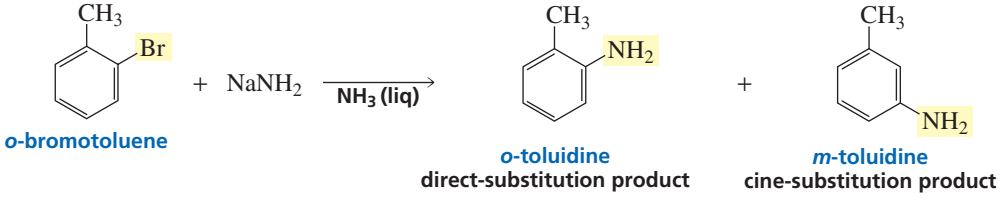
Martin D. Kamen (1913–2002) *was born in Toronto. He was the first to isolate ^{14}C, which immediately became the most useful of all the isotopes in chemical and biochemical research. He received a B.S. and a Ph.D. from the University of Chicago and became a U.S. citizen in 1938. He was a professor at the University of California, Berkeley; at Washington University, St. Louis; and at Brandeis University. He was one of the founding professors of the University of California, San Diego. In later years, he became a member of the faculty at the University of Southern California. He received the Fermi medal in 1996.*

The labeling experiment was done by **John D. Roberts**, *who was born in Los Angeles in 1918. He received both his B.A. and Ph.D. degrees from UCLA. He arrived at the California Institute of Technology in 1952 as a Guggenheim fellow and has been a professor there since 1953.*

The incoming nucleophile can attack either of the carbons of the "triple bond" of benzyne. Protonation of the resulting anion forms the substitution product. The overall reaction is an elimination–addition reaction: Benzyne is formed in an elimination reaction and immediately undergoes an addition reaction.



Substitution at the carbon that was attached to the leaving group is called **direct substitution**. Substitution at the adjacent carbon is called **cine substitution** (cine comes from *kinesis*, which is Greek for "movement"). In the following reaction, *o*-toluidine is the direct-substitution product; *m*-toluidine is the cine-substitution product.



3-D Molecule: Benzyne

Benzyne is an extremely reactive species. In Section 6.3, we saw that in a molecule with a triple bond, the two *sp* hybridized carbons and the atoms attached to these carbons (C—C≡C—C) are linear because the bond angles are 180°. Four linear atoms cannot be incorporated into a six-membered ring, so the C—C≡C—C system in benzyne is distorted: The original π bond is unchanged, but the sp^2 orbitals that form the new bond are not parallel to one another (Figure 16.4). Therefore, they cannot overlap as well as the *p* orbitals that form a normal π bond, resulting in a much weaker and much more reactive bond.

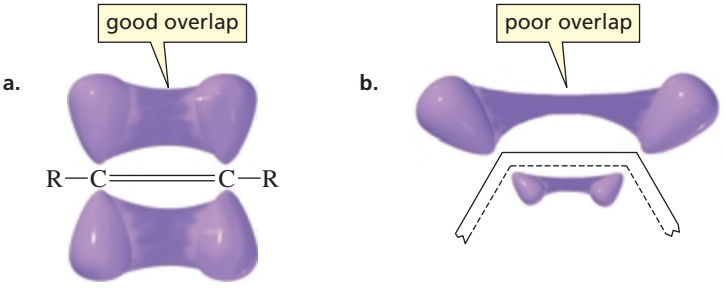
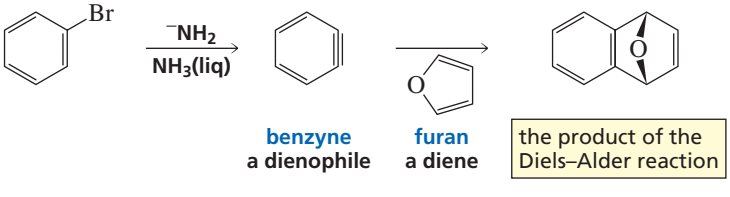


Figure 16.4 ▶
Orbital pictures of the bond formed (a) by overlapping *p* orbitals in a normal triple bond and (b) by overlapping sp^2 orbitals in the distorted "triple bond" in benzyne.

Although benzyne is too unstable to be isolated, evidence that it is formed can be obtained by a trapping experiment. When furan is added to a reaction that forms a benzyne intermediate, furan traps the benzyne intermediate by reacting with it in a Diels–Alder reaction (Section 8.8). The product of the Diels–Alder reaction can be isolated.



A synthesis employing a benzyne intermediate is a good way to prepare *meta*-amino-substituted aryl ethers (see Problem 31). The amide ion preferentially attacks the meta position because there is less steric hindrance at this position and the resulting negative charge can be stabilized by the adjacent electron-withdrawing oxygen atom.

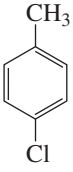
PROBLEM 31

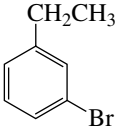
Starting with benzene, show how *meta*-aminoanisole could be prepared via a synthesis that

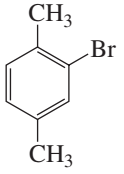
a. involves a benzyne intermediate b. does not involve a benzyne intermediate

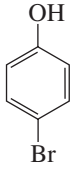
PROBLEM 32

Give the products that would be obtained from the reaction of the following compounds with sodium amide in liquid ammonia:

a. 

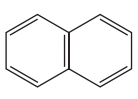
b. 

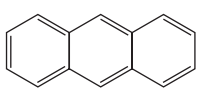
c. 

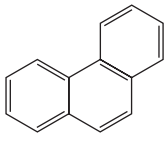
d. 

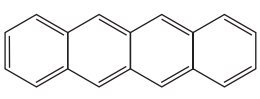
16.15 Polycyclic Benzenoid Hydrocarbons

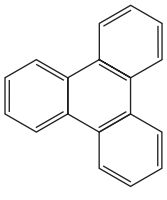
Polycyclic benzenoid hydrocarbons are compounds that contain two or more fused benzene rings. **Fused rings** share two adjacent carbons—naphthalene has two fused rings, anthracene and phenanthrene have three fused rings, and tetracene, triphenylene, pyrene, and chrysene have four fused rings. There are many polycyclic benzenoid hydrocarbons with more than four fused rings.

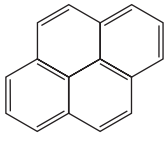

naphthalene

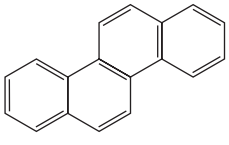

anthracene


phenanthrene


tetracene


triphenylene

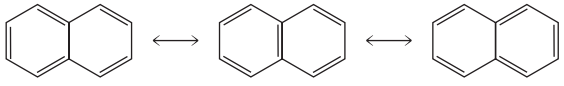

pyrene


chrysene

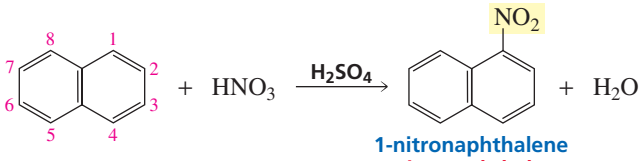
Like benzene, all the larger polycyclic benzenoid hydrocarbons undergo electrophilic substitution reactions. Some of these compounds are well-known carcinogens. The chemical reactions responsible for causing cancer and how you can predict which compounds are carcinogenic were discussed in Section 12.8.

16.16 Electrophilic Substitution Reactions of Naphthalene and Substituted Naphthalenes

Like benzene, naphthalene is an aromatic hydrocarbon. Naphthalene has three resonance contributors.


resonance contributors of naphthalene

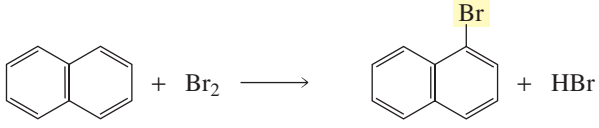
Also like benzene, naphthalene undergoes electrophilic aromatic substitution reactions. Substitution occurs preferentially at the 1-position. In common nomenclature, the 1-position is called the α-position and the 2-position is called the β-position.



1-nitronaphthalene
α-nitronaphthalene

3-D Molecule: Naphthalene

Naphthalene is more reactive than benzene toward electrophilic substitution because the carbocation intermediate is more stable and, therefore, easier to form than the analogous carbocation intermediate formed from benzene. Because of naphthalene's increased reactivity, a Lewis acid is not needed for bromination or chlorination.



1-bromonaphthalene

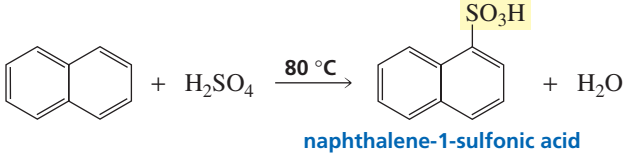
PROBLEM 33

Use the resonance contributors of naphthalene to predict whether all the carbon–carbon bonds have the same length, as they do in benzene.

PROBLEM 34

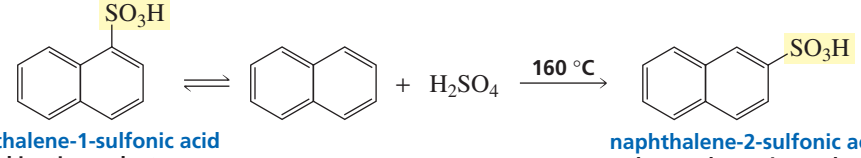
Draw the resonance contributors for the carbocation intermediates obtained from electrophilic aromatic substitution at the 1-position and the 2-position of naphthalene. Use the resonance contributors to explain why substitution at the 1-position is preferred.

Sulfonation of naphthalene does not always lead to substitution at the 1-position. If the reaction is carried out under conditions which cause it to be irreversible (80 °C), substitution occurs at the 1-position.



naphthalene-1-sulfonic acid

If, however, the reaction is carried out under conditions which cause it to be readily reversible (160 °C), substitution occurs predominantly at the 2-position.



naphthalene-1-sulfonic acid
kinetic product

naphthalene-2-sulfonic acid
thermodynamic product

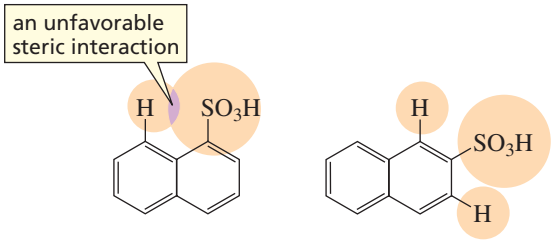
3-D Molecules: Naphthalene-1-sulfonic acid; Naphthalene-2-sulfonic acid

This is another example of a reaction whose product composition depends on whether the conditions used in the experiment cause the reaction to be irreversible (under kinetic control) or reversible (under thermodynamic control). (See Section 8.7.) The 1-substituted product is the kinetic product because it is easier to form. It is the predominant product, therefore, when the reaction is carried out under conditions that cause it to be

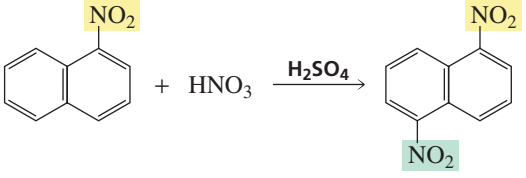
irreversible (mild reaction conditions). The 2-substituted product is the thermodynamic product because it is more stable. It is the predominant product when the reaction is carried out under conditions that cause it to be reversible (higher temperatures).

The 1-substituted product is easier to form because the carbocation leading to its formation is more stable. The 2-substituted product is more stable because there is more room for the bulky sulfonic acid group at the 2-position. In the 1-substituted product, the sulfonic acid group is too close to the hydrogen at the 8-position.

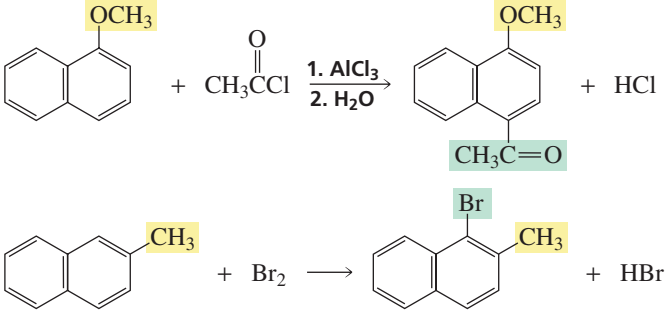
1-Substituted naphthalenes are easier to form; 2-substituted naphthalenes are more stable.



In the case of substituted naphthalenes, the nature of the substituent determines which ring will undergo electrophilic substitution. If the substituent is deactivating, the electrophile will attack the 1-position of the ring that lacks the deactivating substituent, because that ring is more reactive than the ring that contains the deactivating substituent.

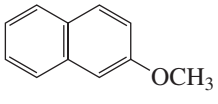


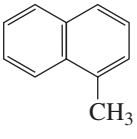
If the substituent is activating, the electrophile will attack the ring that contains the substituent. The incoming electrophile will be directed to a 1-position that is ortho or para to the substituent, because all activating substituents are ortho–para directors (Section 16.4).

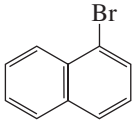


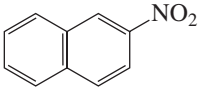
PROBLEM 35

Give the products that would be obtained from the reaction of the following compounds with Cl_2:

a. 

c. 

b. 

d. 

Tutorial:
Terms for the reactions of substituted benzenes

Summary

Benzene rings with substituents other than halo, nitro, sulfonic acid, alkyl, and acyl can be prepared by first synthesizing one of these substituted benzenes and then chemically changing the substituent. The kinds of substituents that can be placed on benzene rings are greatly expanded by reactions of arene diazonium salts, nucleophilic aromatic substitution reactions, and reactions involving a benzyne intermediate. The relative positions of two substituents on a benzene ring are indicated either by numbers or by the prefixes *ortho*, *meta*, and *para*.

The nature of the substituent affects both the reactivity of the benzene ring and the placement of an incoming substituent: The rate of electrophilic aromatic substitution is increased by electron-donating substituents and decreased by electron-withdrawing substituents. Substituents can donate or withdraw electrons **inductively** or by **resonance**.

The stability of the carbocation intermediate determines to which position a substituent directs an incoming electrophile. All activating substituents and the weakly deactivating halogens are **ortho–para directors**; all substituents more deactivating than the halogens are **meta directors**. Ortho–para directors—with the exception of alkyl, aryl, and CH═CHR—have a lone pair on the atom attached to the ring; meta directors have a positive or partial positive charge on the atom attached to the ring. Ortho–para-directing substituents form the para isomer preferentially if either the substituent or the incoming electrophile is large.

In synthesizing disubstituted benzenes, the order in which the substituents are placed on the ring and the point in a reaction sequence at which a substituent is chemically modified are important considerations. When a disubstituted benzene undergoes an electrophilic aromatic substitution reaction, the directing effect of both substituents has to be considered.

RO- and HO-substituted benzenes are halogenated without the Lewis acid. Benzene rings with meta-directing substituents cannot undergo Friedel–Crafts reactions. Aniline and *N*-substituted anilines also cannot undergo Friedel–Crafts reactions.

Aniline and substituted-anilines react with nitrous acid to form **arenediazonium salts**; a diazonium group can be displaced by a nucleophile. Arenediazonium ions can be used as electrophiles with highly activated benzene rings to form **azo compounds** that can exist in cis and trans forms. Secondary amines react with nitrous acid to form **nitrosamines**.

An aryl halide with one or more substituents ortho or para to the leaving group that strongly withdraw electrons by resonance undergoes a **nucleophilic aromatic substitution** (S_NAr) reaction: The nucleophile forms a resonance-stabilized carbanion intermediate, and then the leaving group departs, reestablishing the aromaticity of the ring. The incoming nucleophile must be a stronger base than the substituent being replaced. A substituent that deactivates a benzene ring toward electrophilic substitution activates it toward nucleophilic substitution.

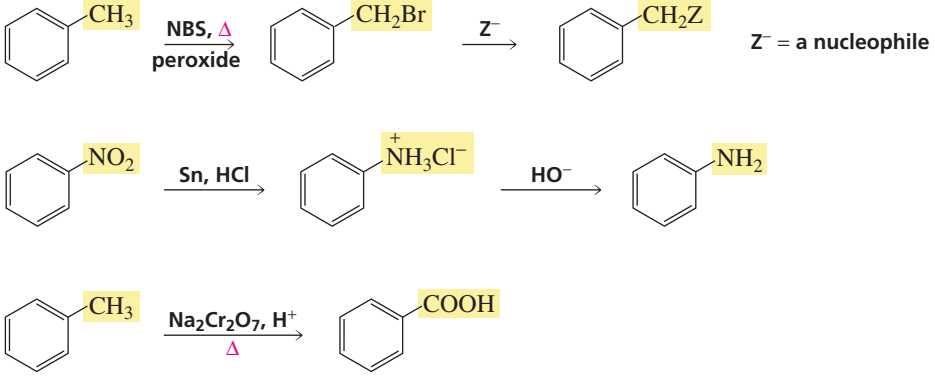
In the presence of a strong base, an aryl halide undergoes a nucleophilic substitution reaction via a **benzyne intermediate**. After a hydrogen halide is eliminated, the nucleophile can attack either of the carbons of the distorted "triple bond" in benzyne. **Direct substitution** is substitution at the carbon that was attached to the leaving group; **cine substitution** is substitution at the adjacent carbon.

The ability of a substituent to withdraw electrons from or donate electrons into a benzene ring is reflected in the pK_a values of substituted phenols, benzoic acids, and protonated anilines: Electron withdrawal increases acidity; electron donation decreases acidity.

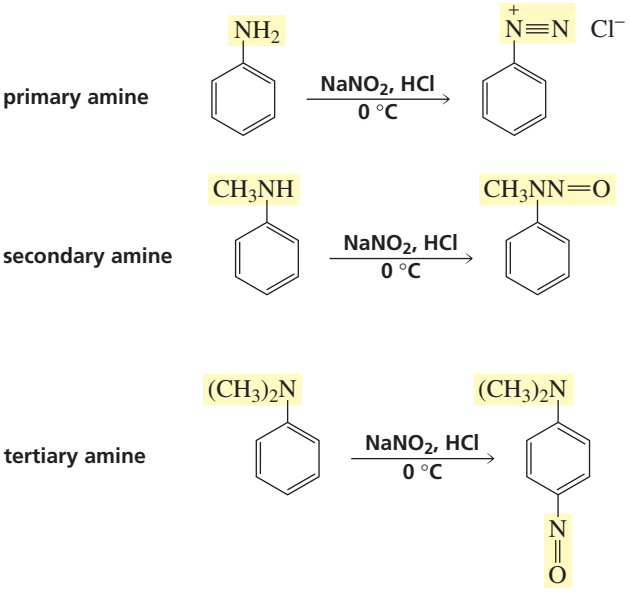
Polycyclic benzenoid hydrocarbons contain two or more fused benzene rings; **fused rings** share two adjacent carbons. Polycyclic benzenoid hydrocarbons undergo electrophilic aromatic substitution reactions. Naphthalene undergoes irreversible substitution predominantly at the 1-position and reversible substitution predominantly at the 2-position. The nature of the substituent determines which ring of a substituted-naphthalene undergoes electrophilic substitution.

Summary of Reactions

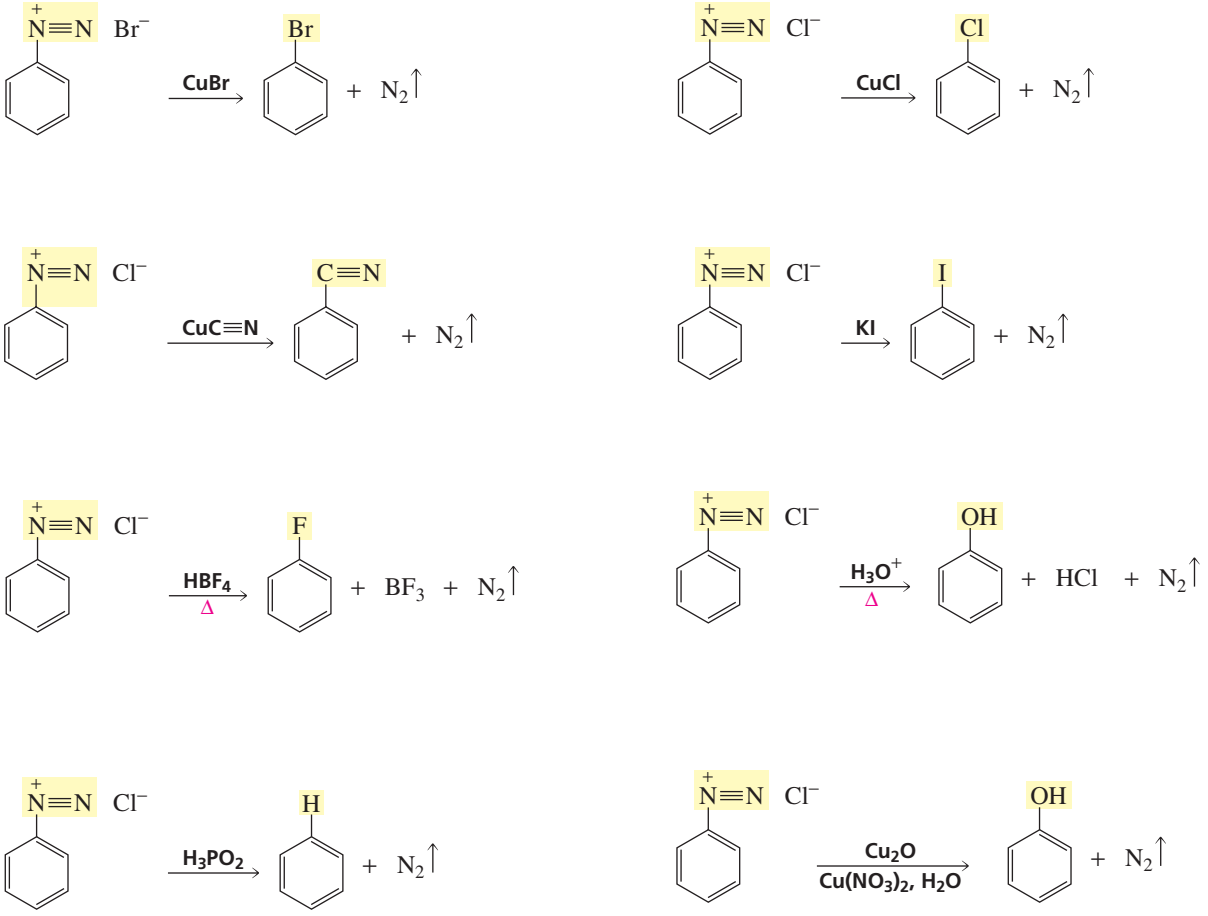
1. Reactions of substituents on a benzene ring (Section 16.2)



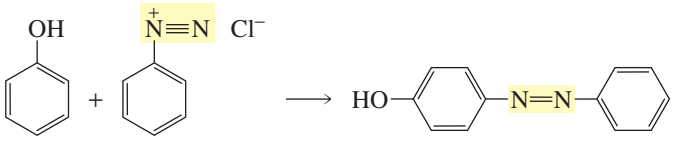
2. Reactions of amines with nitrous acid (Section 16.12)



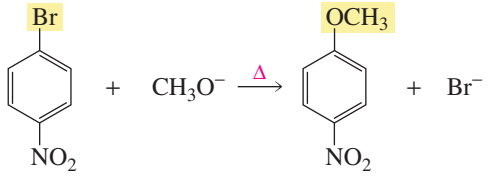
3. Replacement of a diazonium group (Section 16.10)

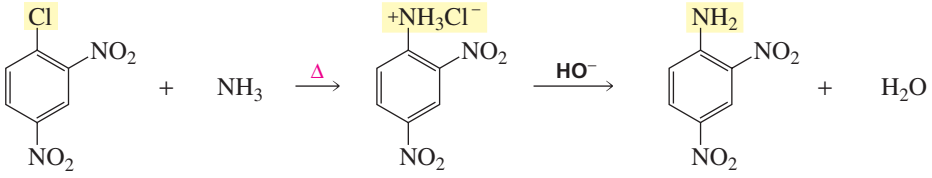


4. Formation of an azo compound (Section 16.11)

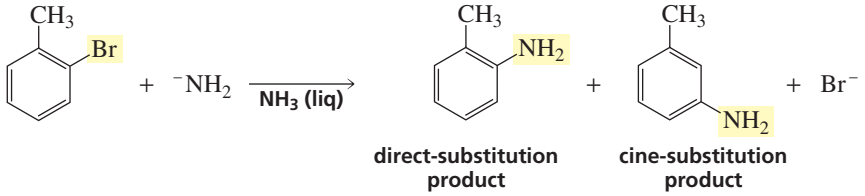


5. Nucleophilic aromatic substitution reactions (Section 16.13)

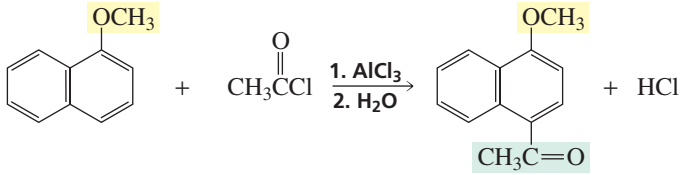


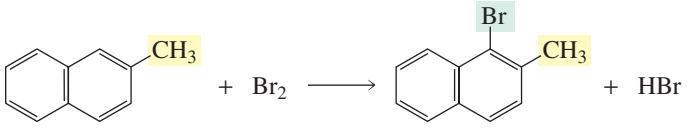


6. Nucleophilic substitution via a benzyne intermediate (Section 16.14)



7. Electrophilic aromatic substitution reactions of naphthalene (Section 16.16)





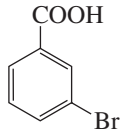
Key Terms

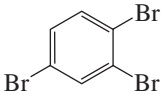
activating substituent (p. 631)
arenediazonium salt (p. 646)
azo linkage (p. 649)
benzyne intermediate (p. 655)
cine substitution (p. 656)
deactivating substituent (p. 631)
direct substitution (p. 656)
donate electrons by resonance (p. 630)
fused rings (p. 657)
inductive electron donation (p. 630)
inductive electron withdrawal (p. 630)
meta director (p. 635)
nitrosamine (p. 651)
N-nitroso compound (p. 651)
nucleophilic aromatic substitution (p. 653)
ortho–para director (p. 635)
resonance electron donation (p. 630)
resonance electron withdrawal (p. 630)
Sandmeyer reaction (p. 646)
Schiemann reaction (p. 648)
S_NAr reaction (p. 654)
withdraw electrons by resonance (p. 631)

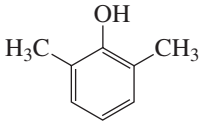
Problems

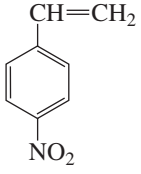
36. Draw the structure of each of the following compounds:
    a. *m*-ethylphenol
    b. *p*-nitrobenzenesulfonic acid
    c. (*E*)-2-phenyl-2-pentene
    d. *o*-bromoaniline
    e. 2-chloroanthracene
    f. *m*-chlorostyrene
    g. *o*-nitroanisole
    h. 2,4-dichlorotoluene

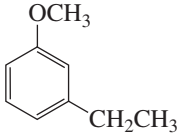
37. Name the following compounds:

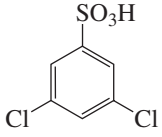
a. 

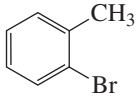
b. 

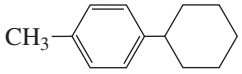
c. 

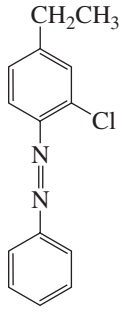
d. 

e. 

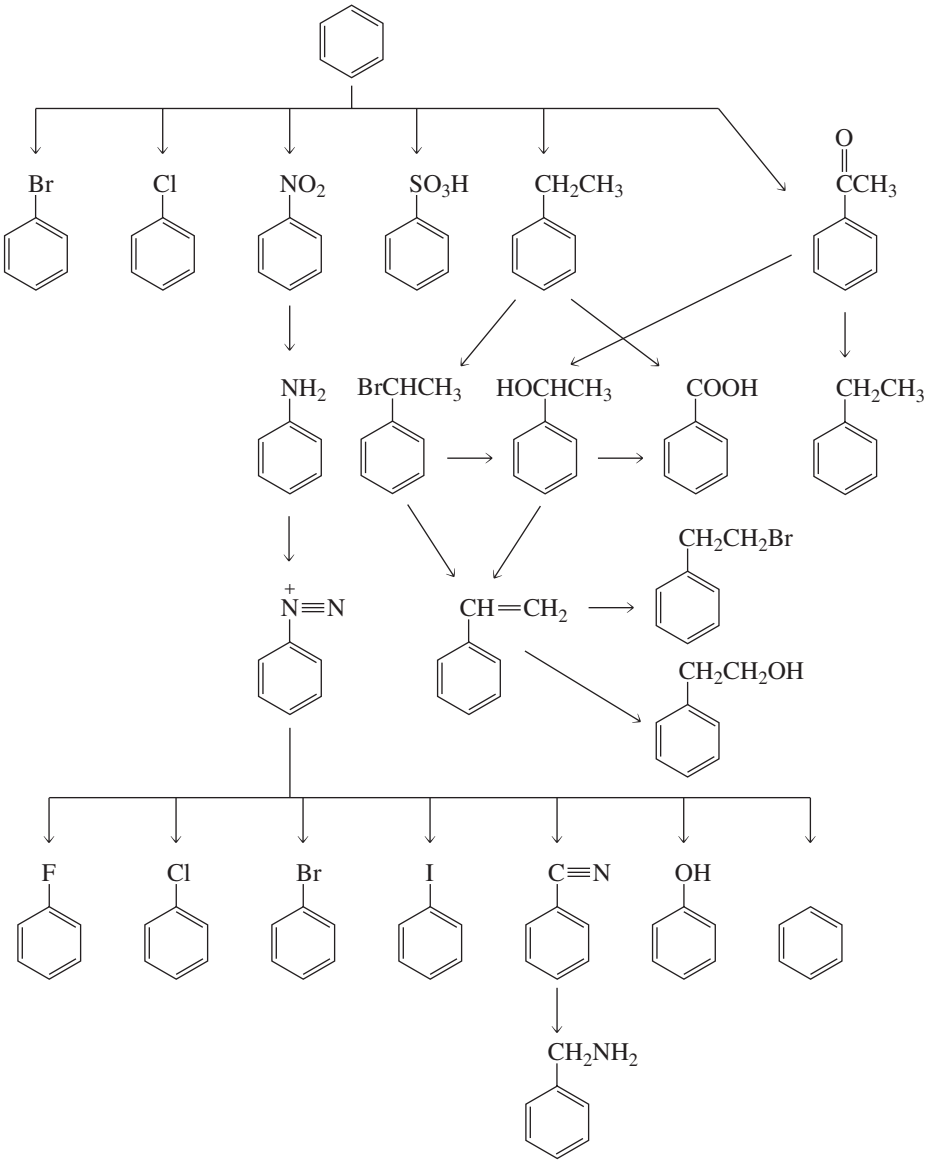
f. 

g. 

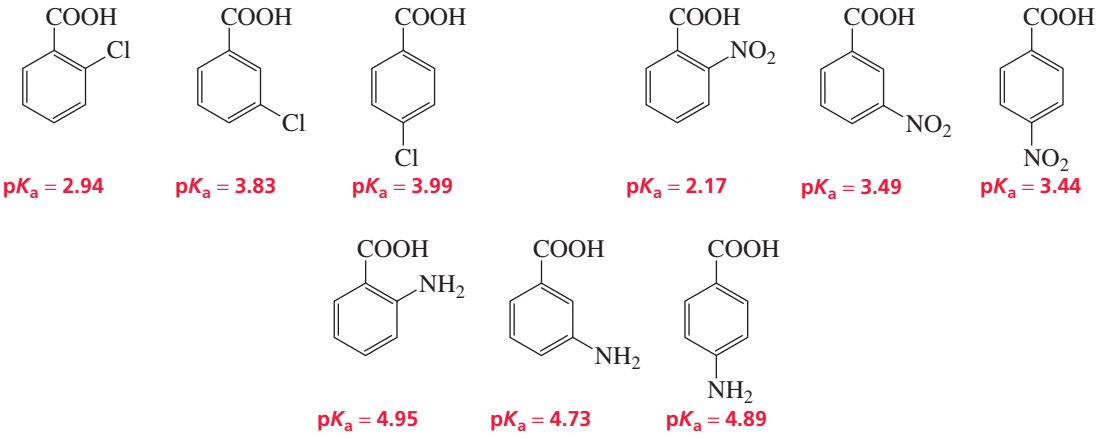
h. 

i. 

38. Provide the necessary reagents next to the arrows.



39. The pK_a values of a few ortho-, meta-, and para-substituted benzoic acids are shown here:



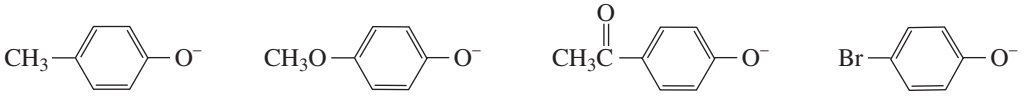
The relative pK_a values depend on the substituent. For chloro-substituted benzoic acids, the ortho isomer is the most acidic and the para isomer is the least acidic; for nitro-substituted benzoic acids, the ortho isomer is the most acidic and the meta isomer is the least acidic; and for amino-substituted benzoic acids, the meta isomer is the most acidic and the ortho isomer is the least acidic. Explain these relative acidities.

Cl: ortho > meta > para NO_2: ortho > para > meta NH_2: meta > para > ortho

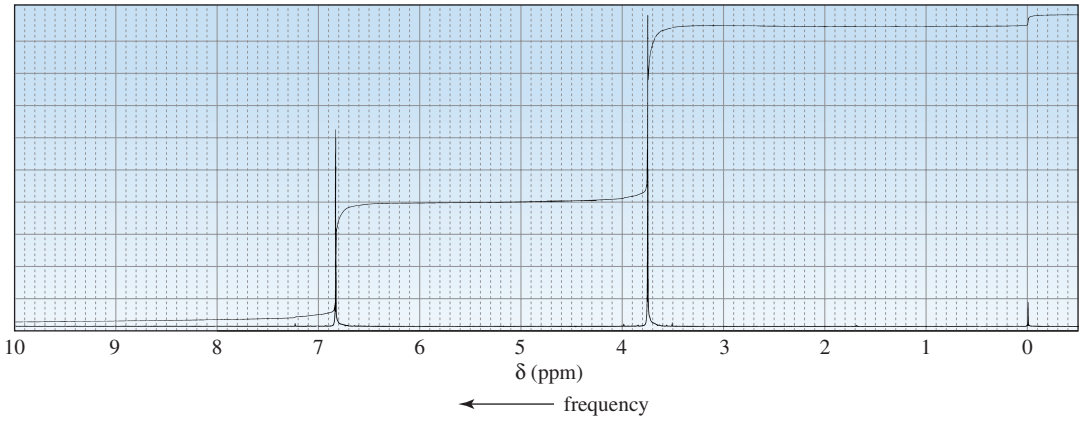
40. Give the product(s) of each of the following reactions:

a. benzoic acid + HNO_3/H_2SO_4
b. isopropylbenzene + cyclohexene + HF
c. naphthalene + acetyl chloride + $AlCl_3$ followed by H_2O
d. *o*-methylaniline + benzenediazonium chloride
e. cyclohexyl phenyl ether + $Br_2/FeBr_3$
f. phenol + H_2SO_4 + Δ
g. ethylbenzene + $Br_2/FeBr_3$
h. *m*-xylene + $Na_2Cr_2O_7$ + H^+ + Δ

41. Rank the following anions in order of decreasing basicity:



42. The compound with the following ^{1}H NMR spectrum is known to be highly reactive toward electrophilic aromatic substitution. Identify the compound.



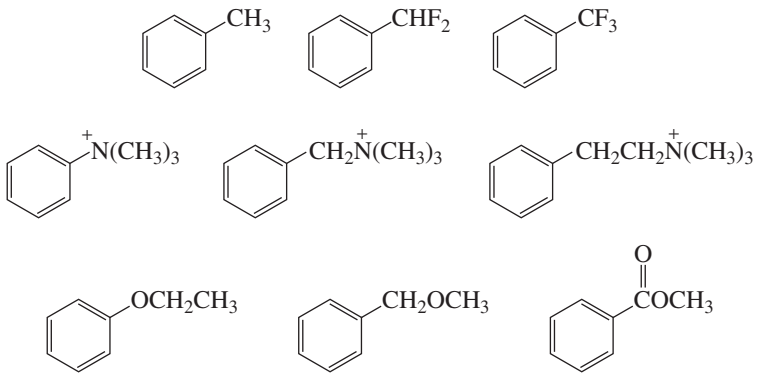
43. Show how the following compounds could be synthesized from benzene:

a. *m*-chlorobenzenesulfonic acid
b. *m*-chloroethylbenzene
c. benzyl alcohol
d. *m*-bromobenzonitrile
e. 1-phenylpentane
f. *m*-hydroxybenzoic acid
g. *m*-bromobenzoic acid
h. *p*-cresol

44. For each of the groups of substituted benzenes, indicate

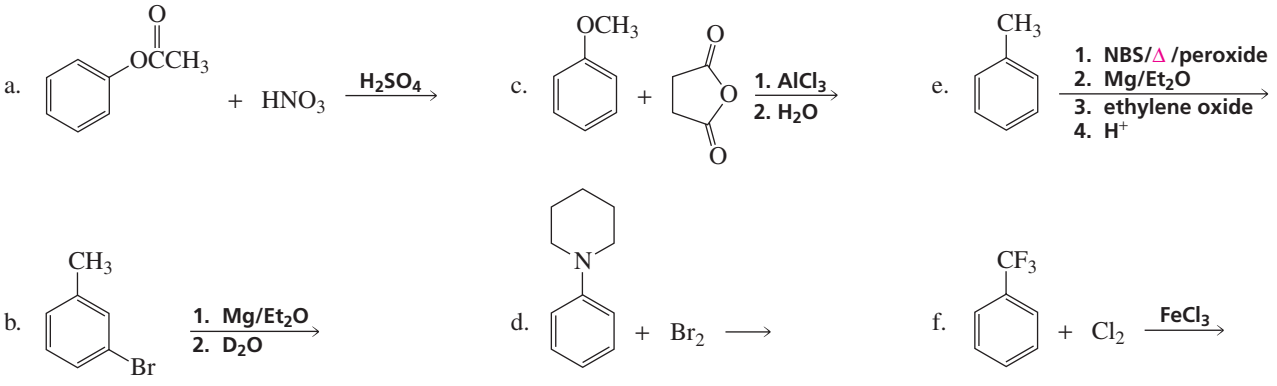
a. the one that would be the most reactive in an electrophilic aromatic substitution reaction

b. the one that would be the least reactive in an electrophilic aromatic substitution reaction
c. the one that would yield the highest percentage of meta product



45. Arrange the following groups of compounds in order of decreasing reactivity toward electrophilic aromatic substitution:
a. benzene, ethylbenzene, chlorobenzene, nitrobenzene, anisole
b. 1-chloro-2,4-dinitrobenzene, 2,4-dinitrophenol, 2,4-dinitrotoluene
c. toluene, *p*-cresol, benzene, *p*-xylene
d. benzene, benzoic acid, phenol, propylbenzene
e. *p*-nitrotoluene, 2-chloro-4-nitrotoluene, 2,4-dinitrotoluene, *p*-chlorotoluene
f. bromobenzene, chlorobenzene, fluorobenzene, iodobenzene

46. Give the products of the following reactions:



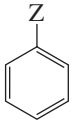
47. For each of the statements in Column I, choose a substituent from Column II that fits the description for the compound at the right:

Column I

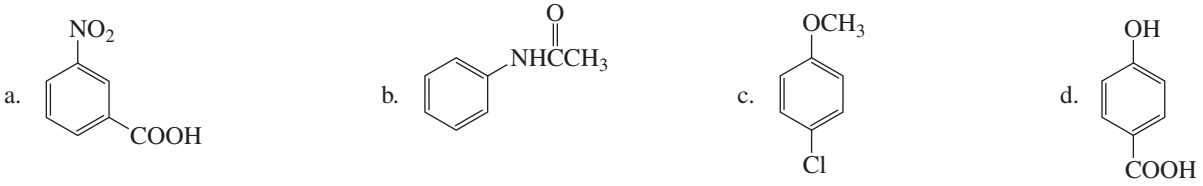
a. Z donates electrons inductively, but does not donate or withdraw electrons by resonance.
b. Z withdraws electrons inductively and withdraws electrons by resonance.
c. Z deactivates the ring and directs ortho–para.
d. Z withdraws electrons inductively, donates electrons by resonance, and activates the ring.
e. Z withdraws electrons inductively, but does not donate or withdraw electrons by resonance.

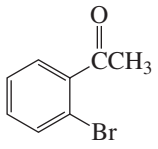
Column II

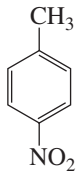
OH
Br
$^{+}NH_3$
CH_2CH_3
NO_2

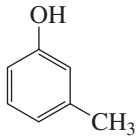


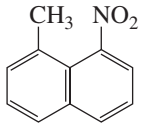
48. For each of the following compounds, indicate the ring carbon that would be nitrated if the compound were treated with HNO_3/H_2SO_4:

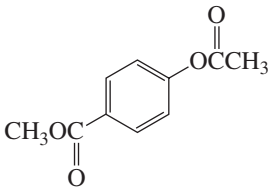


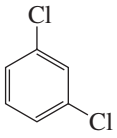
e. 

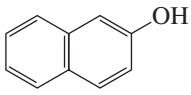
g. 

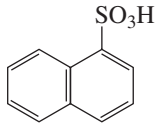
i. 

k. 

f. 

h. 

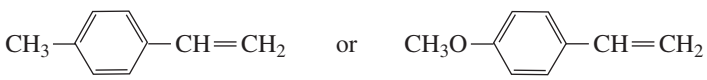
j. 

l. 

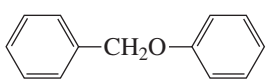
49. Show how the following compounds could be synthesized from benzene:

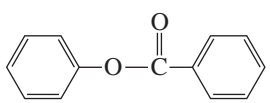
a. *N,N,N*-trimethylanilinium iodide
b. benzyl methyl ether
c. *p*-benzylchlorobenzene
d. 2-methyl-4-nitrophenol
e. *p*-nitroaniline
f. *m*-bromoiodobenzene
g. *p*-dideuteriobenzene
h. *p*-nitro-*N*-methylaniline

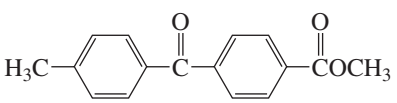
50. Which of the following compounds will react with HBr more rapidly?

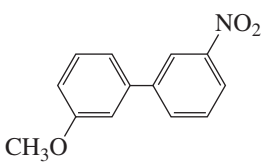


51. Give the product(s) obtained from the reaction of each of the following compounds with $Br_2/FeBr_3$:

a. 

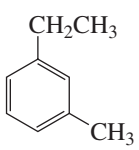
b. 

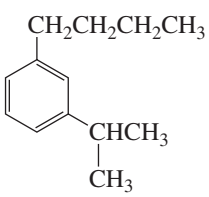
c. 

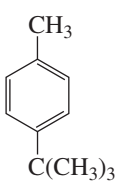
d. 

52. Which would react more rapidly with $Cl_2 + FeCl_3$, *m*-xylene or *p*-xylene? Explain.

53. What products would be obtained from the reaction of the following compounds with $Na_2Cr_2O_7 + H^+ + \Delta$?

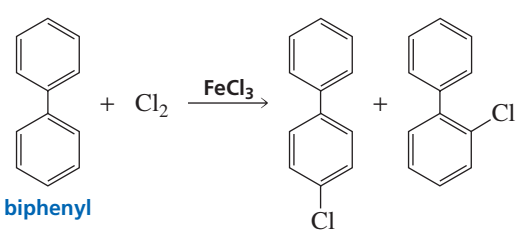
a. 

b. 

c. 

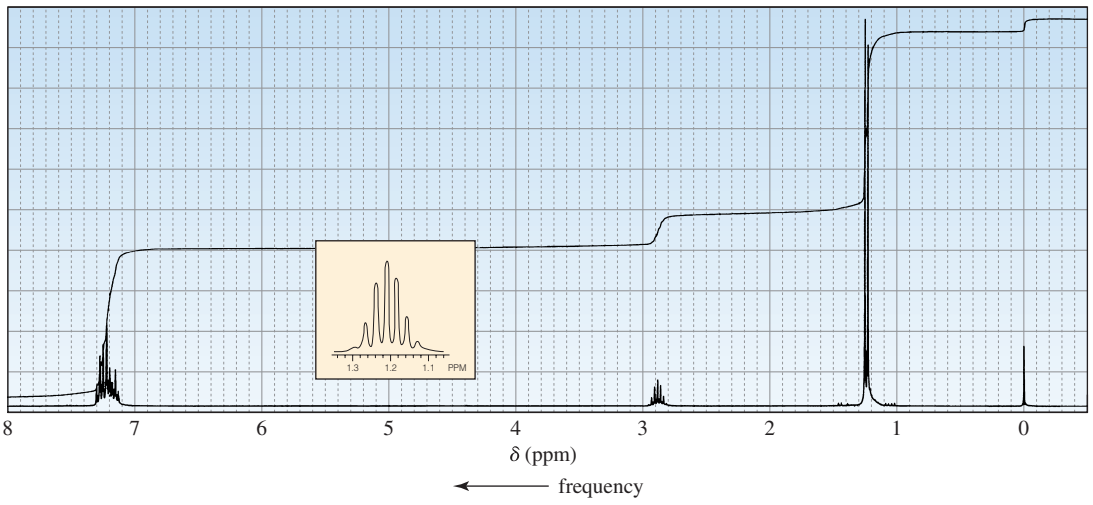
54. A student had prepared three ethyl-substituted benzaldehydes, but had neglected to label them. The premed student at the next bench said that they could be identified by brominating a sample of each and determining how many bromo-substituted products were formed. Is the premed student's advice sound?

55. Explain, using resonance contributors for the intermediate carbocation, why a phenyl group is an ortho–para director.



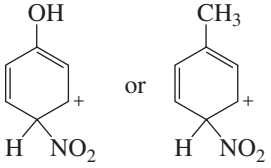
biphenyl

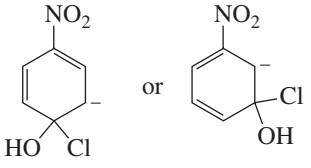
56. When heated with an acidic solution of sodium dichromate, compound A forms benzoic acid. Identify compound A from its ^{1}H NMR spectrum.



57. Describe two synthetic routes for the preparation of *p*-methoxyaniline with benzene as the starting material.

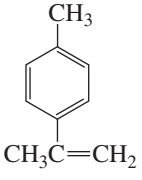
58. Which is a more stable intermediate?

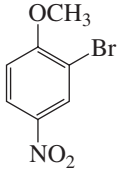
a. 

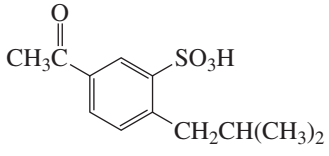
b. 

59. If phenol is allowed to sit in D_2O that contains a small amount of D_2SO_4, what products would be formed?

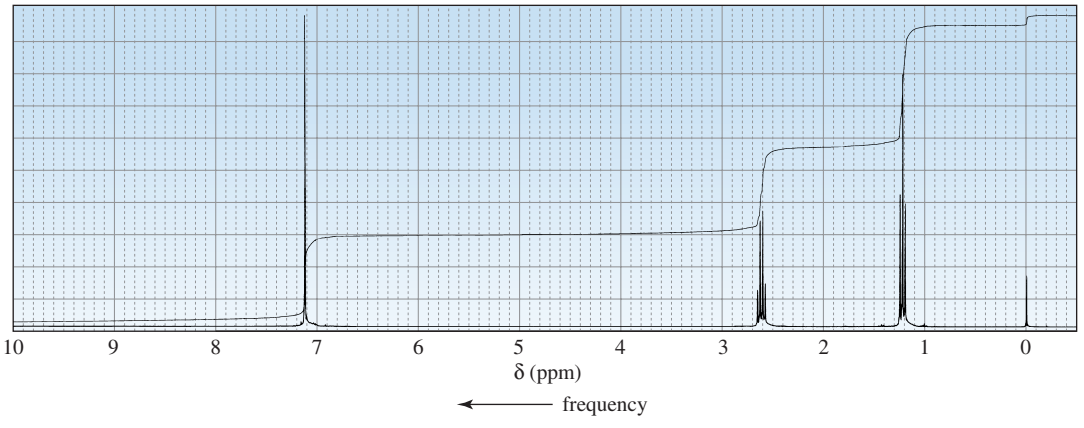
60. Show how the following compounds could be prepared from benzene:

a. 

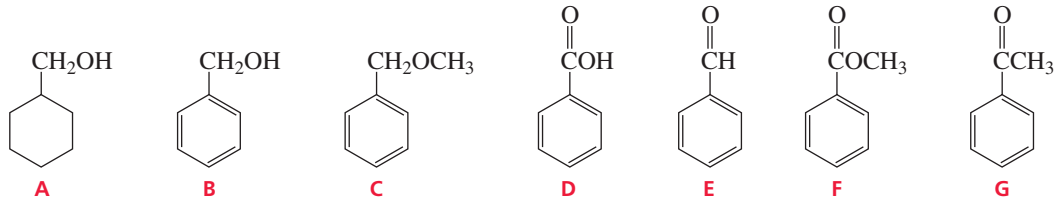
b. 

c. 

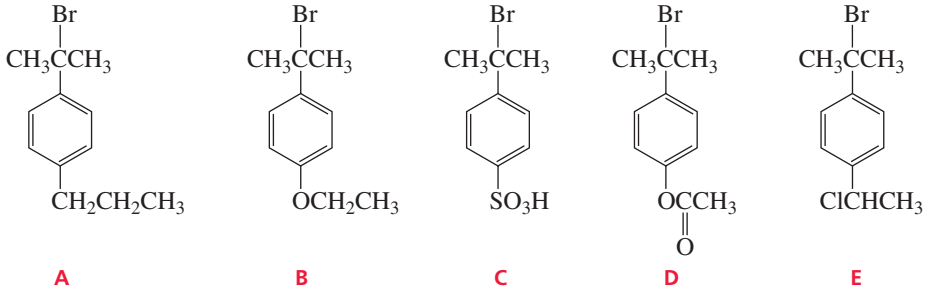
61. An unknown compound reacts with ethyl chloride and aluminum trichloride to form a compound that has the following ^{1}H NMR spectrum. Give the structure of the compound.



62. How could you distinguish among the following compounds, using
    a. their infrared spectra?
    b. their ^{1}H NMR spectra?

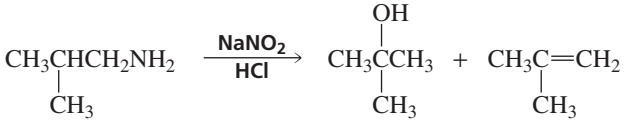


63. The following tertiary alkyl bromides undergo an S_N1 reaction in aqueous acetone to form the corresponding tertiary alcohols. List the alkyl bromides in order of decreasing reactivity.

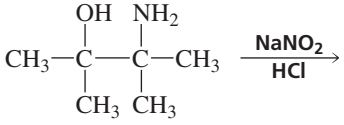


64. *p*-Fluoronitrobenzene is more reactive than *p*-chloronitrobenzene toward hydroxide ion. What does this tell you about the rate-determining step for nucleophilic aromatic substitution?

65. a. Explain why the following reaction leads to the products shown:

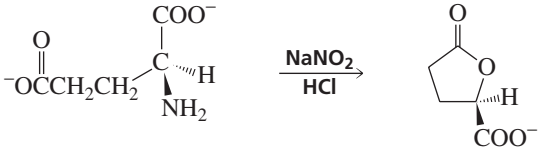


    b. What product would be obtained from the following reaction?

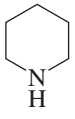


66. Describe how mescaline could be synthesized from benzene. The structure of mescaline is given on p. 622.

67. Propose a mechanism for the following reaction that explains why the configuration of the asymmetric carbon in the reactant is retained in the product:



68. Explain why hydroxide ion catalyzes the reaction of piperidine with 2,4-dinitroanisole, but has no effect on the reaction of piperidine with 1-chloro-2,4-dinitrobenzene.



piperidine